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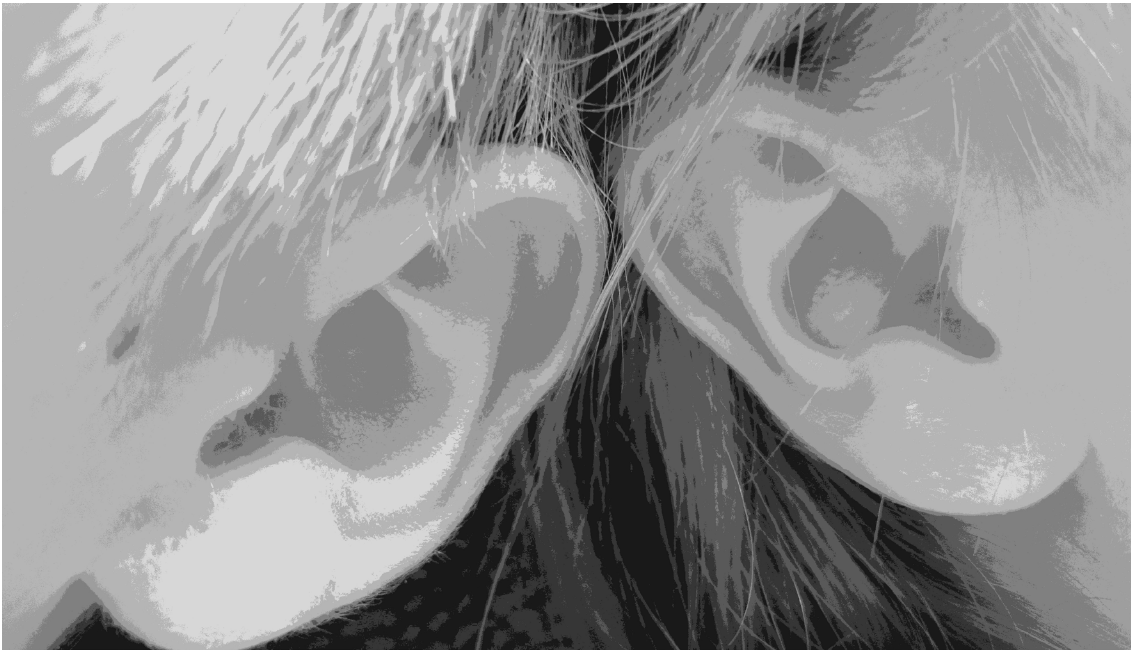
Neurophysiological Conditions for Hearing in Children Using Hearing Aids or Cochlear Implants – An Intervention and Follow-Up Study



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NEUROPHYSIOLOGICAL CONDITIONS FOR HEARING IN CHILDREN USING HEARING AIDS OR COCHLEAR IMPLANTS – AN INTERVENTION AND FOLLOW-UP STUDY

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Neurophysiological Conditions for Hearing in Children Using Hearing Aids or Cochlear Implants – An Intervention and Follow-Up Study

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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Till Kerstin och till minne av Sune

Time flies like an arrow, fruit flies like a banana.

Anthony G. Oettinger,
The Uses of Computers in Science, Scientific American 215:3 (September 1966)

Ett ögonblick kan vara försvinnande kort och ibland vill man bara stoppa tiden.

Den här boken stannar upp vid en bråkdels sekund.

POPULAR SCIENCE SUMMARY OF THE THESIS IN SWEDISH

POPULÄRVETENSKAPLIG SVENSK SAMMANFATTNING

Neurofysiologiska förutsättningar för hörande hos barn som använder hörapparater eller cochleaimplantat – en interventions- och uppföljningsstudie

Det övergripande syftet med projektet var att undersöka de neurofysiologiska förutsättningarna för hörande hos barn med hörapparat eller cochleaimplantat (ett inopererat hörhjälpmedel med elektrisk stimulering av hörselnerven) genom registrering av olika hjärnreaktionspotentialer, så kallade *event-related potentials* (ERP). ERP avspeglar hjärnans elektriska aktivitet kopplad till olika händelser, i detta fall olika ljudstimuleringar.

Barn med hörselnedsättning har visat sig prestera avsevärt sämre än sina hörande kamrater i skolan, trots likvärdiga begåvningsmässiga förutsättningar. Cirka 10 000 barn och ungdomar med hörselnedsättning får idag stöd av hörselvården runt om i landet. Det rör sig således om en stor skara barn, vilket gör det angeläget med forskning på området för att i förlängningen kunna rikta in lämpliga, och gärna individuella, hjälpinsatser. Förhoppningen är att med denna avhandling bidra till en förbättrad situation för barnen med hörselnedsättning.

Ljud- och hörselimpulsernas väg genom ytteröra, mellanöra, inneröra och hörselnerv utreds dagligen vid hörselkliniker runt om i världen. De centrala hörselbanornas funktion och utveckling är däremot inte lika väl kartlagda och förståelsen av dessa är begränsad. Tidigare studier har visat att funktionen av dessa centrala hörselbanor försämras, om de inte får någon stimulans. Formbarheten och känsligheten för stimulering (så kallad *plasticitet*) har setts avta kring sju års ålder, om man ditintills inte fått någon stimulering alls. Detta kan ses som en förklaring till varför barn med medfödd dövhet ofta får svårt att utveckla ett talspråk, om cochleaimplantationen sker efter denna ålder. Idag försöker man således så tidigt som möjligt operera in cochleaimplantat på barn med medfödd dövhet eller grav hörselnedsättning.

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Om hjärnan vore skogen, skulle man kunna tänka sig att de centrala hörselbanorna letar sig fram som stigar där inne bland alla träden. Stigar behöver trampas, annars växer de igen.

Om man hör dåligt, når inte så mycket ljud fram till hjärnan – hörselstigarna stampas därmed inte tillräckligt och grönskan tar vid. Kanske blir det därför också svårare att ta sig fram för det ljud som ändå har kraft nog att alls leta sig in? Kanske hamnar ljudet vilse och man uppfattar det bara som en massa oljud, som är svårt att sätta i sitt sammanhang och som man inte får någon nytta utav?

Det är här handlingen utspelar sig i den här boken – bland de slingriga stigarna i den snåriga skogen.

Event-related potentials och mismatch negativity – bakgrund

ERP-registreringar används ännu inte i den kliniska vardagen inom hörselvården. Nedan följer därför en kort bakgrund och beskrivning av metoden.

Upptäckten av hjärnans elektriska aktivitet tillskrivs den tyske professorn Hans Berger, som 1929 påvisade att elektriska potentialförändringar kan registreras med elektroder placerade på huvudet. Han utvecklade en metod, elektroencefalografi (EEG), som gjorde det möjligt att studera den mänskliga hjärnan hos levande personer. Fortsatt forskning ledde under 1930-talet fram till den första ERP-mätningen med ljudstimuli på en vaken människa. 1964 kunde den första ERP-komponenten påvisas.

Akustisk information från en ton (eller till exempel ett ord) fortleds via hörselbanorna genom hjärnstammen upp till det primära hörselområdet i hjärnbarken, där den sedan kan detekteras på ett medvetet plan. Betydelsen av den akustiska informationen kan dock inte tolkas förrän informationen nått sekundära hörsel- och språkliga associationsområden i hjärnan. Genom registrering av ERP, som görs genom elektroder ytligt mot skalpen, kan man följa nervaktiviteten i hjärnan. Tidiga komponenter, synliga som vågor på en ERP-registrering, utgör ett mått på hörselsystemets förmåga att notera ljud och påverkas främst av stimulus fysikaliska egenskaper medan senare komponenter avspeglar en mer komplex bearbetning av ljud som engagerar sekundära och associativa hörselcentra.

Mismatch negativity (MMN), förmågan att uppfatta små ljudkontraster som är viktiga för att förstå tal, upptäcktes 1978 av en finländsk psykolog och forskare inom neurovetenskap, Risto Näätänen. MMN betraktas som en förmedveten, icke påverkbar process, som inte kräver aktiv lyssning. För att beräkna MMN jämförs ERP-svaret av standardstimulus med ett avvikande stimulus (*deviant*) som orsakar ett starkare ERP-svar, när det uppfattas av hörselcentra. Man får då en så kallad *mismatch*. MMN är således differenskurvan av ERP-svaren mellan ett avvikande stimulus och standardstimulus.

MMN-registreringarna var länge tidskrävande med mätning av en *deviant* åt gången men Risto Näätänen och hans medarbetare har vidareutvecklat en mer tidseffektiv metod, Optimum 1, där fem olika *devianter* (gap/uppehåll i ljudet, intensitet/styrka, frekvens/tonhöjd, lokalisation och duration/varaktighet) varvas med standardstimulus. Metoden kan ses som lämplig för barn, eftersom ERP-tekniken är icke-invasiv, ofarlig, inte kräver aktiv lyssning och är relativt snabb.

ERP och MMN får idag anses vara etablerade forskningsmetoder och det finns riktlinjer för hur registreringar ska utföras samt flera läroböcker på området. Dock används olika MMN-modeller i olika forskargrupper. Exempelvis kan olika karaktär på stimuli och *devianter* användas, liksom olika antal elektroder. Bearbetning av data behöver genomgå flera olika steg, till exempel hopsamling av data, filtrering, segmentering och artefaktbearbetning. Detta kan vara utfört på olika sätt i olika studier. Själva beräkningen av MMN ger likaså möjligheter till olika analyser, bland annat kan man välja mellan beräkning av topp- eller medelamplitud, latens eller area (*area under curve*). Val av tidsfönster varierar och ibland baseras resultaten av en visuell bedömning av kurvorna. Sammantaget kan det vara svårt att jämföra resultat från olika studier.

En utmaning är att MMN genomgår en mognadsprocess under barndomsåren, vilket komplicerar analyser och tolkningar av resultaten. Det finns studier som talar för att MMN till och med uppvisar positiva svar, så kallade *positive mismatch responses* (pMMR).

Deltagarna – projektets huvudpersoner

I projektet deltog sammanlagt 46 barn: 30 barn med hörselnedsättning (15 barn med hörapparater och 15 barn med cochleaimplantat) samt en kontrollgrupp med 16 barn, som var normalhörande. I analyserna delades barnen med hörselnedsättning upp i två undergrupper; en hörapparat-grupp respektive en cochleaimplantat-grupp. Det blev därmed tre likstora grupper. Barnen var fem till sju år gamla, när den första delstudien startade.

Projektets metod och utformning – kan hörseln tränas och vad händer när man växer upp?

Projektet innefattar fyra delstudier och designen gällande hela projektet var delvis experimentell, eftersom liknande studier i stort sett saknas på denna patientgrupp. Den första delstudien, **delstudie I**, undersökte om metoden med ERP-registreringar och MMN alls gick att genomföra på barn som använde sina hörhjälpmedel, det vill säga om det skulle gå att mäta upp ERP och MMN hos barn som samtidigt använde sina hörapparater eller cochleaimplantat. Åldersmatchade normalhörande kontrollbarn deltog. Hypotesen var att man skulle kunna mäta upp skillnader i svaren på ERP och MMN mellan grupperna, eftersom barn med hörselnedsättning antas ha sämre förmåga att uppfatta små ljudkontraster.

Delstudie II och III var utformade som interventionsstudier, där ett internetbaserat fonologiskt (språkligt) träningsprogram (GraphoGame), som tränar kopplingen mellan ljud och bokstäver, förväntades ha en positiv effekt på barnens hörselförmåga. Hypotesen var att detta också skulle kunna uppmätas med ERP-registreringar och MMN. Interventionsprogrammet genomfördes dagligen under en månads tid i barnens hem. Utifrån åldersgruppen bedömdes en månads träning vara rimlig för följsamheten och det ansågs inte föreligga någon risk för påverkan av MMN:s mognadsprocess under denna tidsperiod.

ERP-registreringar utfördes omedelbart före och direkt efter interventionen. Det hade varit önskvärt att ha en kontrollgrupp utan träning men grupperna var från början relativt små och därtill ville alla deltagande familjer få ta del av träningsprogrammet. Därav deltog en jämförelsegrupp med åldersmatchade, normalhörande barn.

Den avslutande treårsuppföljningen utgjorde den sista och fjärde delstudien, **delstudie IV**. I denna undersöktes hur ERP och MMN förändrades över tid i samtliga tre grupperna.

Ett elektrodnät med 129 elektroder användes vid samtliga registreringar, även vid treårsuppföljningen. Samtliga delstudier i detta projekt analyserades, processades och bearbetades på samma sätt i EP Toolkit, MATLAB®. Cochleaimplantat orsakar en speciell störning (artefakt) i ERP-vågorna, vilket krävde ett extra moment i databearbetningen av dessa barn. Statistiska beräkningar gjordes i SPSS®, i första hand *repeated measures ANOVA*. Data analyserades individuellt, för varje enskild *deviant* men resultaten är huvudsakligen presenterade på gruppnivå och inom tidsintervallet 80–224 millisekunder efter stimuli.

Resultat

Delstudie I visade att ERP-svar och MMN kunde erhållas i samtliga grupper. Barnen med hörapparat fick generellt lägre ERP-amplituder jämfört med övriga grupper. Svaren från de olika *devianterna* var svårvärderade. Delstudien ledde till uppstrukturering av ERP-kurvorna, vilket kom att ligga till grund för bearbetning och analyser i de kommande delstudierna. Det visade sig att pMMR var vanligt förekommande bland alla deltagande barn, vilket försvårade analyser och tolkning av resultaten.

I **delstudie II** sågs skillnader i ERP-svar och MMN mellan barnen med hörapparat och de normalhörande barnen före träning med GraphoGame men att dessa skillnader mellan grupperna försvann efter träning. Det skulle kunna tala för att träningsprogrammet vore av värde för barnen med hörapparat.

Delstudie III kunde inte visa liknande resultat efter träning för barnen med cochleaimplantat, vilket synliggjorde skillnader mellan undergrupperna av barn med hörselnedsättning.

I både **delstudie II och III** förelåg en betydande blandning av pMMR och MMN hos varje enskilt barn och därtill en stor individuell variation i hur dessa förändrades efter träning.

Delstudie IV kunde demonstrera en förändring av ERP-svaren efter tre år hos barnen med hörapparater. Det fanns också en skillnad mellan barnen med hörapparat och barnen med normal hörsel vid första ERP-mätningen men vid treårsuppföljningen saknades den skillnaden. Det skulle kunna innebära att barnen med hörapparat kommit ikapp en del. Barnen med cochleaimplantat fick däremot svagare ERP-svar efter tre år, vilket skulle kunna tyda på en sämre utveckling av de centrala hörselbanorna hos dessa barn. Sammantaget skulle således detta kunna tala för att, å ena sidan, barnen med hörapparat har förutsättningar för att tillgodogöra sig träningsinsatser även uppåt i åldrarna (åtta till elva år i denna studie), å andra sidan, att barnen med cochleaimplantat kan ha större svårigheter och kräver utökat stöd.

I samtliga delstudier är det värt att poängtera att en försiktighet med tolkningarna av resultaten är motiverad. Materialet är litet och endast små individuella skillnader är att vänta i ERP-svar och MMN vid exempelvis träning och uppföljning över tid. Detta innebär begränsningar i att statistiskt kunna påvisa eventuella effekter. Med andra ord kan träningsprogrammet vara gynnsamt även för barnen med cochleaimplantat men underlaget är således för litet för att säkert kunna uttala sig om detta. Med detta sagt kan nämnas att andra studier visat fördelar med träningsprogrammet hos normalhörande barn med till exempel dyslexi och att det inte finns skäl att tro att språkträningen skulle ha några särskilda negativa konsekvenser. Det är också värt att komma ihåg att samtliga delstudier har fokus på specifikt neurofysiologiska mätningar och resultat av ERP och MMN. Avslutningsvis bör också understrykas att träningsprogrammet bör ses som ett eventuellt komplement – och inte som en ersättning – till andra insatser från exempelvis hörselvård, logopeder, skola och föräldrar.

I övrigt kan det också finnas intressanta kopplingar till exempelvis ålder, grad av hörselnedsättning, orsak, tid för hörapparatanpassning respektive cochleaimplantation. I dessa delstudier gick inte sådana eventuella samband att statistiskt påvisa i någon större utsträckning men vore intressanta att analysera i ett större material.

Klinisk relevans och framtidsperspektiv

MMN-tekniken är ofarlig, icke-invasiv och kräver inte någon aktiv medverkan, vilket utgör några av metodens styrkor. Därtill gör utvecklingen av en förhållandevis snabb registrering (Optimum-1) att metoden lämpar sig för både klinik och undersökning av barn.

Då MMN avspeglar diskriminationsförmåga skulle det kunna bli ett värdefullt objektivt kvalitetsmått och en hjälp till professionen att på ett tidigt stadium fånga upp de barn som kan behöva extra hjälpinsatser, träning och stöd. Kanske kan det på sikt också bidra till att individanpassa olika träningsmetoder och vägleda hur olika hjälpmedel behöver vidareutvecklas. Ytterligare kartläggning behövs, för att se om någon eller några *devianter* är bättre än andra på att avspegla olika svårigheter eller skillnader mellan grupperna och i olika åldrar. Det skulle även kunna vara av värde att undersöka senare ERP-svar på likartat sätt.

Inom audiologin skulle MMN-registreringar i framtiden också kunna bli ett tillskott som en objektiv mätmetod till sedvanliga psyko-akustiska (beteendemässiga) mätmetoder (vanliga hörselprov, såsom tonaudiogram och talaudiogram). Det kan framför allt vara av värde för barn som har svårt att medverka vid tester, till exempel de yngsta barnen samt hos barn med olika funktionsnedsättningar. Man kan även tänka sig ERP- och MMN-registreringar som ett komplement vid utredning av barn med annat hemspråk, där olika talaudiometrier inte kan utföras.

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Sammanfattningsvis baseras merparten av resultaten på hur hjärnan hos barn med hörselnedsättning uppfattar små skillnader av fem olika ljud i ett tidsintervall mellan ungefär 100 och 200 millisekunder efter ljudstimuleringen. I sammanhanget kan 0,1 sekunder kanske verka både kort eller långt.

Resultaten får betraktas som ledtrådar i jakten på att lösa hela hörselgåtan men det är inte säkerställt exakt vilken betydelse dessa har eller om en pusselbit är viktigare än någon annan. Den individuella blandningen av MMN- respektive pMMR-svar var överraskande stor och till synes oförutsägbar. Mer forskning behövs för att lägga klart pusslet och för helhetsbilden behöver det sannolikt betraktas från flera professioner och ur olika perspektiv. Kanske gömmer sig någonstans *The Perfect Mismatch*.

Förhoppningsvis kan denna avhandling också inpspirera fler forskningsintresserade att våga sig in i detta delvis outforskade och utmanande område. Välkomna!

ABSTRACT

OBJECTIVES

The four studies in this thesis examine the central auditory pathways in children with hearing loss (HL) through recording event-related potentials (ERP) and mismatch negativity (MMN). The design of the project is partly experimental, and it also includes an intervention part and a follow-up-study after three years. The primary aims were the following:

I. Explore whether a multi-feature paradigm (Optimum-1) for eliciting MMN could characterise difficulties in perceiving small sound contrasts in children with HL using their hearing aids (HAs) or cochlear implants (CIs) (**Paper I**).

II. Investigate whether a computer-assisted reading intervention programme with a phonics approach (GraphoGame) could affect ERP and MMN in children with HL using HAs (**Paper II**) and CIs (**Paper III**).

III. Examine the developmental changes of ERP and MMN over time (three years) among children with HL using HAs or CIs (**Paper IV**).

METHODS

In total, children with HL (n=30) using HAs (n=15) or CIs (n=15), as well as a reference group of children with normal hearing (NH) (n=16), participated. All children were approximately 5–8 years old at baseline (the first ERP recording session), and 8–11 years old at the follow-up after three years.

Paper I includes all participants at baseline.

Paper II (children with HAs) and **Paper III** (children with CIs) are the intervention part: one month of repeatedly training with a computer-assisted reading intervention programme with a phonics approach (GraphoGame) and involve two ERP recording sessions: before and after the training.

Paper IV comprises the follow-up study after three years and includes all three groups: the children using HAs, the children with CIs, and the children with NH.

All studies are based on ERP recordings that, including the data processing, were identical for each of the three sessions.

The ERP-recordings followed the multi-feature paradigm, Optimum-1. Thus, a standard stimulus alternated among five different deviants (gap, intensity, pitch, location, and duration), presented in a pseudorandom sequence. MMN was calculated from the average ERP of each deviant minus the standard stimulus. Analysis of variance (ANOVA) was used for the statistical analyses. **Paper I** served as a model for analyses and interpretations of the results. The results in **Paper II–IV** were based on samples within a specific time interval: 80–224 ms.

The method is non-invasive and safe for the participants. MMN is independent of attention, measured by using an electrode net. Optimum-1 enables short recording sessions. Together, it is a method appropriate for testing children.

RESULTS

Paper I demonstrated that the multi-feature paradigm, Optimum-1, could elicit responses in children with HL using their HAs or CIs. Four time windows (TW) were created to structure and facilitate further analyses. TW 2 of 80–220 ms was considered appropriate for the primary test of MMN effects. Overall, the response amplitudes were smaller in the HA group than the NH groups in TW 2. Otherwise, the results could not statistically prove any major differences in discrimination between groups.

Paper II established significant differences in the obligatory responses in both ERP and MMN between the NH and HA groups before the computer-assisted training, which disappeared after the intervention. This suggests possible training effects among the children with HAs. This paper also provides a description of MMN and positive mismatch response (pMMR) in all deviants and groups (NH vs HA).

Paper III could not statistically demonstrate any computer-assisted training effects detectable with ERPs and MMN among children with CIs. Thus, the results differ from the results regarding children with HAs in **Paper II**, suggesting that there are differences between these two subgroups of children with HL. The paper also offers a description of MMN and pMMR regarding all deviants in each group (NH vs CI).

Paper IV found a significant difference in mean ERP at baseline compared to the time of follow-up three years later in the HA group. This suggests a possible catch-up over time among the children with HAs. On the contrary, the obligatory responses in ERP among the children with CI were significantly lower than both the children with NH and HAs after three years, indicating impaired development of the central auditory system among the children with CIs.

There was a high degree of inter-individual variability of both MMNs and pMMRs due to maturational changes in the current age groups. Only small changes were to be expected after training (**Paper II and III**) and after follow-up (**Paper IV**), which, together with small sample sizes, may have diminished the ability to demonstrate significant results.

LIST OF SCIENTIFIC PAPERS

I. Using a multi-feature paradigm to measure mismatch responses to minimal sound contrasts in children with cochlear implants and hearing aids
Uhlén I, Engström E, Kallioinen P, Nakeva von Mentzer C, Lyxell B, Sahlén B, Lindgren M, Ors M
Scand J Psychol. 2017 Oct; 58(5):409-421

II. Computer-assisted reading intervention for children with sensorineural hearing loss using hearing aids: Effects on auditory event-related potentials and mismatch negativity
Engström E, Kallioinen P, Nakeva von Mentzer C, Lindgren M, Ors M, Sahlén B, Lyxell B, Uhlén I
Int J Pediatr Otorhinolaryngol. 2019 Feb; 117:17-25

III. Computer-assisted reading intervention for children with hearing impairment using cochlear implants: Effects on auditory event-related potentials and mismatch negativity
Engström E, Kallioinen P, Lindgren M, Nakeva von Mentzer C, Sahlén B, Lyxell B, Uhlén I
Int J Pediatr Otorhinolaryngol. 2020 Oct; 137:110229

IV. Auditory event-related potentials and mismatch negativity in children with hearing loss using hearing aids or cochlear implants – a three-year follow-up study
Engström E, Kallioinen P, Nakeva von Mentzer C, Magnus Lindgren†, Sahlén B, Lyxell B, Ors M, Uhlén I
†Deceased in August 2020.
Int J Pediatr Otorhinolaryngol. 2021 Jan; 140:110519

CONTENTS

LIST OF ABBREVIATIONS

ABR	Auditory brainstem response
ANOVA	Analysis of variance
ANSD	Auditory neuropathy spectrum disorders
CAEP	Cortical auditory evoked potential
CI	Cochlear implant
CNC	Cochlear nucleus complex
Cz	Central zero (central electrode in the midline)
dB	Decibel
DCN	Dorsal cochlear nucleus
EEG	Electroencephalogram
ERP	Event-related potential
Fz	Frontal zero (frontal electrode in the midline)
HA	Hearing aid
HL	Hearing loss
IC	Inferior colliculus
ICA	Independent component analysis
MMN	Mismatch negativity
NH	Normal hearing
OAE	Otoacoustic emission
PCA	Principal component analysis
pMMR	Positive mismatch response
PTA	Pure tone average
SNHL	Sensorineural hearing loss
SOC	Superior olivary complex
TW	Time window

1 INTRODUCTION

The overall aim of this thesis was to learn more about children with hearing loss (HL) and, in the longer term, contribute to their enhanced support, for example, at the audiological, pedagogical, and speech and language pathology services. The studies focused on the central auditory pathways by recording the event-related potentials (ERP) and mismatch negativity (MMN). ERP recordings are still not used in clinical practice but are an established research method today. However, the neurophysiological field is complex, and the method implies several options regarding the choice of stimuli, processing, analyses, and interpretations of the results, resulting in the experimental design of this project.

To start, the method was tested in children with HL, when using their hearing aids (HAs) or cochlear implants (CIs) (**Paper I**). The hypothesis was that the computer-assisted reading intervention programme with a phonics approach, GraphoGame, could improve the ability to hear and discriminate small changes in the auditory stimulation, and that these changes would be detectable by ERP and MMN (**Paper II and III**). Finally, ERP and MMN undergo maturational changes during life (Cheour et al., 1998; Draganova et al., 2005; Morr et al., 2002; Shafer et al., 2010). Thus, a three-year follow-up study was performed, to examine how ERP and MMN change and develop over time among children with HL (**Paper IV**).

Thus, children with HL using HAs or CIs, ERP recordings, and the computer-assisted reading intervention programme (GraphoGame), constitute the three main parts of this project. Background to each topic follows in the next Section, *2 Literature review*, starting with the protagonists in this thesis – the children with HL.

However, first a summary about the auditory system, as an initial indicator of where this thesis will take place.

1.1 THE AUDITORY SYSTEM

The auditory system begins with the peripheral auditory system, which consists of the external ear, the middle ear, the inner ear, and the cochlear nerve (Nervus Cochlearis, or the cochlear branch of cranial nerve VIII). The auricle of the external ear collects the sound waves and amplifies the sound energy of frequencies important for speech. The sound waves are then directed through the external auditory canal to the tympanic membrane. The middle ear is a space filled with air and contains three small ossicles: malleus, incus, and stapes. The sound waves pass along the ossicles and reach the inner ear through the oval window. Due to the small footplate of the stapes, compared to the size of the tympanic membrane, the energy overcomes the impedance from the air-filled space between the middle ear and the external auditory canal to the fluid-filled inner ear. (Katz et al., 2002).

Together, the vestibular system and the cochlea form the inner ear. The cochlea is a tube divided longitudinally into three parallel sections: scala vestibuli, scala media, and scala tympani. Movement of the footplate causes a pressure wave in the scala vestibuli, leading to vibrations of the basilar membrane and bending of stereocilia on top of receptor cells; the inner and outer hair cells, in the organ of Corti. The cochlea is about 30 mm long and coiled into a 2¾ turn spiral in a tonotopic arrangement; the base for high-frequency stimuli and the apex for low-frequency stimuli. In the cochlea, the mechanical vibrations from the soundwaves are transformed into nerve impulses. These nerve impulses are then transmitted to the central auditory pathways by the cochlear nerve. (Katz et al., 2002).

The cell bodies of the afferent fibres are found in the spiral ganglion. The afferent fibres leave the inner ear through the internal auditory canal and enter the brainstem at the level of the cerebellopontine angel and terminate in the cochlear nucleus complex (CNC), where the central auditory system and neuronal processing begins. The tonotopic arrangement is preserved along the nerve and in the CNC. The CNC consists of three nuclei: the dorsal cochlear nucleus (DCN), the anteroventral cochlear nucleus, and the posteroventral cochlear nucleus. The two latter ones form the ventral cochlear nucleus. Some of the axons from the CNC decussate in the trapezoid body to the contralateral side before continuing to the superior olivary complex (SOC). This organization probably helps with localization of sound. SOC is closely related to the trapezoid body and consists of several nuclei important for the auditory system. Through a tract of axons in the brainstem, the lateral lemniscus, the CNC and SOC is connected to the inferior colliculus (IC) of the midbrain. The central nucleus of the IC is believed to integrate information, such as sound source localization from the SOC (Oliver, 2000) and DCN, before the auditory data is further transmitted to the medial geniculate body of the thalamus and, finally, the primary auditory cortex, which is thought to identify basic characteristics of sound. Only when the auditory sensations are received and processed by a cortical area, they reach perception. (Katz et al., 2002).

After reaching the brain, the complexity of the auditory system increases, and the cortical pathways are still not fully understood. For years, research has been based on information obtained from animal studies; however, the anatomy of the human brain differs from that of the animal brain. Behavioural studies and advanced methods, such as positron emission tomography (also known as PET), functional magnetic resonance imaging (also known as fMRI), and evoked potential recordings, have enabled mapping the activity of the brain. (Katz et al., 2002). One of the ERP components, the MMN, is thought to reflect the activity in the auditory cortex (Garrido et al., 2008; Parras et al., 2017), see *2.2.2 Mismatch negativity (MMN)* below. Based on results from the aforementioned methods, certain parts of the brain are generally accepted as important for the central auditory pathways, and the most well-known areas are mentioned in the following paragraphs.

Hearing is important for speech and language development, and the auditory cortex is connected to, and interacts, with parts of the cerebral cortex linked to speech, such as Wernicke's area and Broca's area. The auditory cortex, including Brodmann areas 41 and 42, is bilaterally part of the temporal lobe that processes auditory information from both ears. It extends into the lateral sulcus and the transverse temporal gyrus, also called the Heschl's gyrus. Tonal stimulation activates only a small area within Heschl's gyrus. More complex stimuli, for example, noise, phonemes and words, cause more activation in the superior temporal gyrus. (Katz et al., 2002).

Heschl's gyrus is surrounded by the temporal plane, the posterior superior temporal gyrus (Brodmann area 22), the angular gyrus (Brodmann area 39), the supramarginal gyrus (Brodmann area 40) and the insula. In the left cerebral hemisphere, Brodmann area 22 is a part of Wernicke's area and helps with understanding and generation of words. On the right side of the brain, Brodmann area 22 assists in the perception of melody and prosody by discriminating pitch and sound intensity. Furthermore, a tonotopic organization has also been demonstrated in the auditory cortex and in Brodmann area 22 (Katz et al., 2002; Lutkenhoner & Steinstrater, 1998; Pantev et al., 1989).

The auditory cortex transmits signals and interconnects with other parts of the cortex, including areas important for comprehension and articulatory networks (Hickok & Poeppel, 2015; Katz et al., 2002). Thus, the auditory cortex should not be considered as the endpoint of a sound stimulus. However, the auditory cortex is the area of focus in this thesis.

Figure 1 provides an illustration of parts of the peripheral and central auditory system.

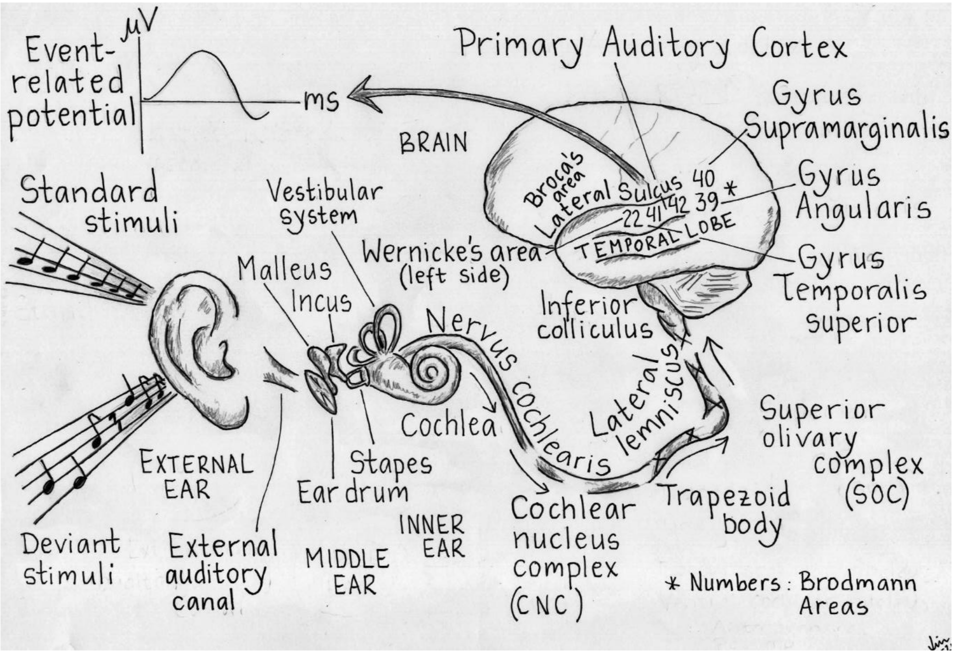


Figure 1. *Illustration of the peripheral and central auditory system, including stimuli eliciting event-related potentials. (Illustration by Elisabet Engström.*)

2 LITERATURE REVIEW

2.1 CHILDREN WITH HEARING LOSS

2.1.1 Hearing loss

Several pathological conditions may cause hearing impairment in childhood. Briefly, conductive HL results from disorders involving structures of the external and middle ear, sensory HL involves disorders in the cochlea, and the neural hearing disorders result from complications involving the auditory nervous system. Sensorineural hearing loss (SNHL) is a wider term, fusing the two latter types of HL.

In children, even mild HL can have a large impact on the development of speech and language; the effects of HL are much more significant for children than for adults. Not only is the type and degree of HL important, but also the configuration, stability, and time when the HL occurs. (Bluestone et al., 1996; Dimitrov & Gossman, 2020; Madell & Flexer, 2013). Furthermore, HL can be monaural or binaural.

The degree of HL is often categorised on a scale from mild, moderate, severe to profound (Clark, 1981), based on the average of the hearing thresholds in decibel (dB) from pure tones at 0.5, 1.0, 2.0 and 4.0 kHz, known as the pure tone average (PTA; or PTA4, if referring to the average of the four aforementioned frequencies). For example, the configuration of the audiogram can depict a high-, mid-, low-frequency HL, or (more seldom) a flat loss, but the PTA is coarse and only offers a fragmentary description of the HL. The PTA does not specify the type or cause of HL, meaning the impact of hearing quantity only (basically conductive HL), or additional quality impairment (sensorineural HL). *Figure 2* provides an overview of an audiogram with the different degrees of HL and points out the four frequencies forming the PTA4. *Table 1* describes possible difficulties reported in adult patients with HL, according to the degree of HL. Applying these criteria to young children poses a challenge because HL in children is complicated by the associated effects of stunted speech and language development. In clinical practice, a delay in speech and language usually requires examinations of the hearing.

In summary, the PTA values capture some of the difficulties, and possible suffering, a child with HL may experience, but cannot depict the entire individual hearing situation.

When phonemes (the sounds of speech) are plotted on an audiogram, they form a banana-shaped region (Andersson & Arlinger, 2007) called the *speech banana (Speech Banana Audiogram)*. This region covers the sound magnitude and frequencies needed to understand most sounds of average conversational speech. In the light of the *speech banana*, the pure tone audiometry gives a picture of what difficulties HL might cause.

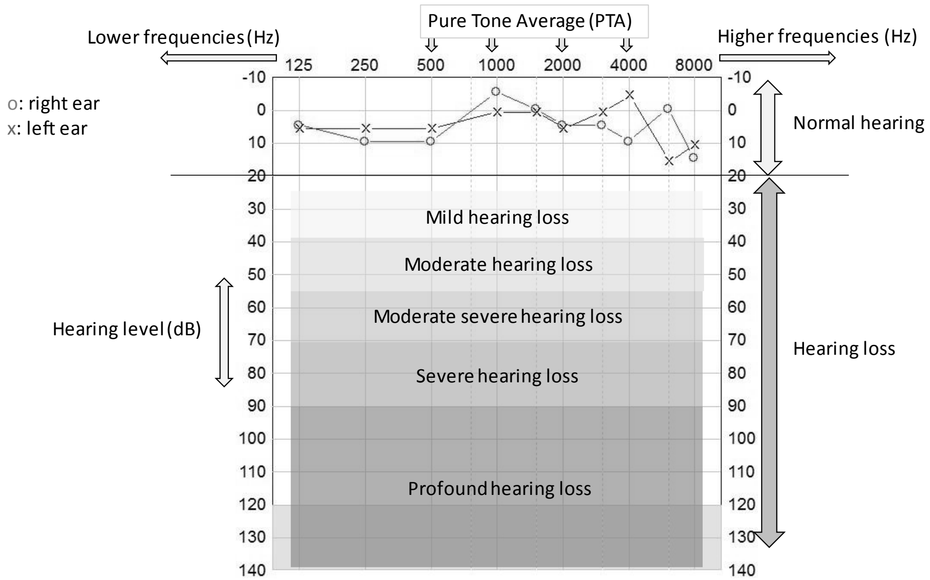


Figure 2. The audiogram, an overview. Normal hearing (air conduction in a fictional patient plotted in AuditBase) and degrees of hearing loss. Hz, hertz; dB, decibel. (Illustration by Elisabet Engström.)

Table 1. Hearing situations following different degrees of hearing loss in adult patients.

Categories of HL	Pure tone average	Difficulties; examples
Mild HL	26–40 dB	One-on-one conversations may be easy, but it is difficult to keep up with conversations in noisy surroundings.
Moderate HL	41–55 dB	Without hearing aids, it is difficult to keep up with conversations and phone calls. Lots of speech sounds are missing and it is often necessary to ask for others to repeat themselves.
Moderate severe HL	56–70 dB	Without hearing aids, it is difficult to keep up with conversations → Powerful hearing aids are needed, but even when using hearing aids, lip-reading is essential for conversations.
Severe HL	71–90 dB	Powerful hearing aids are needed, but even when using them, lip-reading is essential for conversations. Sign language may be beneficial. Using telephones will be exceedingly difficult. Cochlear implants may be an alternative.
Profound HL	>90 dB	Conversations mostly rely on lip-reading and/or sign language. Hearing aids are insufficient. To perceive speech sounds, cochlear implants may be an alternative.

Pure tone average (PTA): the average of the hearing thresholds at 0.5, 1.0, 2.0 and 4.0 kHz and level of stimuli presentation (dB hearing level). The categories of hearing loss (HL) follow the classification by Clark (Clark, 1981). Examples are adapted from European Group on Genetics of Hearing Impairment. Martini A, ed. European Commission Directorate, Biomedical and Health Research Programme (HEAR) Infoletter 2, November 1996;8. (Table compiled by Elisabet Engström.)

2.1.2 Hearing tests in children

The appropriate hearing assessment techniques for children vary depending on age, cognitive level, and cooperation. Above all, these prerequisites are important to consider, when using different behavioural hearing and psychoacoustic tests. However, objective hearing tests are also used in clinical practice, such as the evoked otoacoustic emission (OAE) test. The OAE test is easily and quickly performed and detects the outer hair vibrations in response to a click stimulus. The OAE test is used in many new-born hearing screening programmes worldwide. Testing the auditory brainstem responses (ABR) is usually performed when a child does not pass the OAE test. ABR measures the electrophysiological responses to click stimuli and assesses hearing all way through the brainstem. A few electrodes are placed on the scalp during the ABR test. ABR measurement is sensitive to the effects of movements, causing movement artefacts, and is therefore preferably measured while the child is asleep. Today, a time-saving automated ABR is often used as a first step, when the OAE test fails. Auditory steady-state response (ASSR) may also be used for threshold estimation in infants, requiring the same preconditions as ABR. (Dimitrov & Gossman, 2020; Madell & Flexer, 2013).

For clinical use, ABR is the most common auditory evoked responses recorded in children. Evoked responses represent a summed auditory neural activity. The waveforms are usually described in terms of latency and amplitude of the peaks, and they also contain ‘electrical noise’. The latency range of ABR is within the first 10–15 ms. In addition to the hearing screening of new-borns and estimation of pure tone hearing thresholds, ABR is used for investigation of retrocochlear pathology and auditory neuropathy spectrum disorders (ANSD). A few other examples of auditory evoked responses are the electrocochleogram (ECoG; latency range: 0–3 ms; used in the investigation of ANSD), the middle-latency response (MLR, also called middle-latency potential; latency range: around 10–50 ms; used for assessment of the central auditory function), cortical auditory evoked potentials (CAEP; latency range: 50–400 ms; used in the evaluation of HAs or evaluation of hearing, when ABR is unreliable). (Dimitrov & Gossman, 2020; Luck, 2014; Luck & Kappenman, 2011; Madell & Flexer, 2013).

Different behavioural hearing tests are dependent on the response from the individual being tested and involve distraction techniques, such as BOEL test (gaze orientation by sound; from Swedish *‘blicken orienterar efter ljud’*) (Junker et al., 1978) (around 6–8 months of age), visual reinforcement audiometry (around 9 months–3 years), conditioned play audiometry (around 2–5 years), and pure tone audiometry (from around 5 years and up). Pure tones (sinusoidal waveforms, single frequencies) are used to test air and bone conduction. (Dimitrov & Gossman, 2020; Madell & Flexer, 2013).

Word intelligibility tests (speech discrimination tests) provide information about the auditory functioning and assess the central auditory processing. Children over 7 years old can usually perform word intelligibility tests designed for adults, but there are also tests developed for younger children. However, these tests have their own limitations. It is essential to select an appropriate test for the vocabulary level of each child. Moreover, poor articulation may affect the test scores, meaning it may be difficult to value the answers from a child, who cannot correctly pronounce the words. (Bluestone et al., 1996; Dimitrov & Gossman, 2020; Katz et al., 2002; Madell & Flexer, 2013).

2.1.3 Children with hearing loss

In Sweden, around 1–4 per 1 000 babies are born with HL that will require assistance from the health care system (*Coordination, Responsibility and Communication – The Road to Increased Quality for Students with Disabilities (SOU 2016:46).* 2016; Mäki-Torkko & Jönsson, 2006). The prevalence of permanent childhood hearing impairment is nearly consistent with results from studies regarding neonatal hearing screening in other countries, for example, in the United Kingdom (Fortnum et al., 2001) and in Colorado, U.S.A (Dimitrov & Gossman, 2020; Mehl & Thomson, 2002). Minor differences might be due to differences in the case definition. In addition, there are children with acquired or progressive HL, or HL with later onset. The Swedish children start school the year they turn 6 years, and compulsory school the year they turn 7 years. Around this time, the number of children with HL needing assistance, meaning using HAs, CIs or sign language, doubles to 2–8 per 1 000 (*Coordination, Responsibility and Communication – The Road to Increased Quality for Students with Disabilities (SOU 2016:46).* 2016; Uhlen et al., 2020). An increased prevalence of hearing impairment is similarly reported in the United Kingdom, with 50–90% increase of the number of children diagnosed with permanent HL by the age of 9 years (Fortnum et al., 2001). The Swedish audiology and habilitation centres assist nearly 10 000 children and adolescents (0–20 years old) with HL or deafness, according to the Swedish patient organisation, *Hörselskadades Riksförbund* (HRF) (*Leva med hörselnedsättning och dövhet - Att växa upp som hörselskadad eller döv*). Around 3 000 children in Sweden are estimated to need technical support and adjustments in the elementary school (6–15 years). However, HRF call attention to undetected children, and the schools are reporting that around 4 000 children need support (*Coordination, Responsibility and Communication – The Road to Increased Quality for Students with Disabilities (SOU 2016:46).* 2016).

Since 1990, children with congenital deafness are offered CIs in Sweden. Today, around 70–75 children undergo CI surgery in Sweden each year, half of them (around 40) at the Department of ENT at Karolinska University Hospital in Stockholm.

Among the children needing assistance, a cochlear HL, commonly referred to as SNHL, is more common than conductive HL. SNHL is usually considered as permanent, and thus, will follow through life. Sometimes, the SNHL is progressive and regular testing is of importance. This means, a child initially helped with HAs might develop a profound HL needing CIs later.

Children with HL often perform less well academically compared to children with normal hearing (NH), despite equal learning capacity (*Coordination, Responsibility and Communication – The Road to Increased Quality for Students with Disabilities (SOU 2016:46).* 2016; Hendar, 2008, 2012). In preschool children with a moderate-to-severe SNHL, speech and language development are delayed by 1.5–2 years (Borg et al., 2007), and phonological impairment is seen in nearly half of the children with mild-to-moderate SNHL (Briscoe et al., 2001). Using HAs or CIs will not fully compensate for the deprivation of auditory developmental processes.

Several parameters may affect the hearing experience. Aetiology, degree of HL, affected frequencies, age at diagnosis, age at HA fitting and CI surgery may differ considerably among the children with HL. The HL can be congenital (thus, also pre-lingual), progressive or later acquired. Children with congenital deafness have a defined onset of hearing at the activation of the CI, whereas the other children with HAs or CIs can have various degree of hearing ability before receiving their hearing devices. Early or late diagnosis does not necessarily mean low or high age at HA fitting or CI surgery. Thus, the *hearing age* might differ in the same chronological age group. This possible heterogeneity must be kept in mind, when studying children with HL, and when interpreting hearing data. The new-born hearing screening programmes will certainly contribute to the overall knowledge of the hearing history from birth.

2.1.4 Hearing aids and cochlear implants

Devices facilitating the hearing situation for persons with HL once started with the ear trumpets and date back to the 17th century. These ear trumpets did not amplify sound but worked by collecting and funnelling the sound into the ear. The first electric HA was created by Miller Reese Hutchison in 1898 (Mills, 2011). Gradually, the devices have become more successful with better technology and smaller sizes. The development of the analogue HAs to the digital devices was initiated during the Second World War, however, the first wearable digital HA was not developed until the 1980s (Levitt, 2007). Today, small devices suitable for infants are available.

Regarding CIs, the first attempt to electrically stimulate the human auditory system was performed by André Djourno and Charles Eyriès in 1957, however, this was not successful (Djourno & Eyries, 1957). Only four years later, in 1961, the otologist Dr William F. House, together with the neurosurgeon Dr Doyle, achieved more promising results with some basic frequency discrimination (Doyle et al., 1963). However, the electrodes were still simple and there were complications with infections and device rejection. An electrical engineer, Mr Urban, contributed to the further development of the CIs in 1967 (House & Urban, 1973), as well as the NASA engineer Adam Kissiah in the 1970s. The modern multi-channel CI was independently developed by two separate teams; Ingeborg and Erwin Hochmair in Austria implanted their first device in 1977, and Dr Graeme Clark in Australia the year after (Clark et al., 1978). Later, device improvements have enabled patients to recognise speech and even enjoy music. By 1990, the first young infants (2 years of age) were implanted. (Clark, 2006; Eshraghi et al., 2012).

Still, the deprivation of auditory developmental processes remains among children with HL and cannot, despite the improving technology, be fully compensated by HAs or CIs. Thus, it is important to identify the children who need extra support and help them enhancing their phonological processing ability.

2.2 EVENT-RELATED POTENTIALS AND MISMATCH NEGATIVITY

2.2.1 Event-related potentials

2.2.1.1 A short background

In 1929, the German professor Hans Berger first measured the electrical activity of the human brain – this was the beginning of the electroencephalogram (EEG) (Berger, 1929). This made it possible to study the brain in living humans. First, researchers believed the observed brain waves were artefacts. A few years later, in 1935, Jasper (Jasper & Carmichael, 1935) confirmed the utility of EEGs.

In 1939, Davis published the results of acoustic stimuli on the conscious human brain (Davis, 1939). The first cognitive ERP component was reported 25 years later, in 1964 (Walter et al., 1964). A negative voltage (contingent negative variation) was thought to reflect the preparation for the upcoming stimulus rather than be just a sensory response. Following this, ERP was mostly used in cognitive experiments, and research was focused on discovering and understanding the ERP components. For example, the P3 component was described in 1965 by Sutton, which was published in *Science* (Sutton et al., 1965).

2.2.1.2 Neurophysiology – a brief introduction and summary

With electrodes placed along the surface of the scalp, EEG monitors and records voltage fluctuations from ionic currents in the brain. EEG can record spontaneous electrical activity and neural oscillations (so called 'brain waves'). Electrical responses, also known as potentials, which are related (or 'time-locked') to specific, sensory events, are called ERPs. These ERPs are possible to extract from the overall EEG.

So called *dipoles* are created by negative charges at the apical dendrites versus positive charges at the cell bodies. When many neurons summate, it is possible to measure these dipoles through the resulting voltage at the scalp. The ERP waveforms are based on postsynaptic potentials in large groups of cortical pyramidal cells and form peaks, which vary in polarity (positive or negative waves), amplitude (usually measured in microvolt, µV), and latency (milliseconds, ms). Furthermore, ERP waveforms reflect the difference in activity between an active and a reference site. In cognitive neuroscience, the most common reference sites are the earlobes or the mastoid processes, also known as the mastoid reference. Thus, the ERP waveform become differently prominent depending on the scalp position and choice of reference site. (Luck, 2014; Luck & Kappenman, 2011).

The ERP technique is non-invasive and safe. ERP-recordings provide a measure of the ability of the auditory system to detect sound. The P1-N1 complex, meaning the first positive and negative peaks, is elicited by external stimuli. Later components, such as P300 (or P3) and N400 are positive and negative peaks around 300 versus 400 ms after the auditory stimuli and reflect a more complex processing of sound, which affects the secondary auditory centre. (Luck, 2014; Luck & Kappenman, 2011). The auditory sensory responses are summarised and presented in *Table 2* below.

Table 2. *The auditory sensory responses, an overview and compilation based on ERP textbooks (Luck, 2014; Luck & Kappenman, 2011).*

Auditory sensory responses	**Peaks, waves or components and polarity**	**Position or latency**	**Dependence on external or internal factors**
ABR (auditory brainstem responses)	Waves I–VI	0–10 ms	External, such as click
MLR (middle latency responses)		10–50 ms	Possible influences by attention
Long-latency responses		50–160 ms Each peak last for 10–20 ms	Exogenous but influenced by attention
	P1 (P50)	50 ms	Exogenous
	N1 (N100)	100 ms	Exogenous
	P2 (P160)	160 ms	Exogenous
MMN (mismatch negativity) or pMMR (positive mismatch response)	*Deviant-minus-standard difference wave*	*160–220 ms*	*Automatic response*
‘High level cognitive components’			
	N2 (N200)	Around 200–350 ms	Endogenous
	P3 (P300)	Wide range of latencies, often between 350 and 600 ms. Peak may last for >100 ms	Endogenous, ‘Cognitive peak’
Language-related ERP (event-related potential)			
	N400	Second major negative component. Peaks around 380–440 ms.	Endogenous

P, positive; N, negative; ms, milliseconds. (Table compiled by Elisabet Engström.)

2.2.1.3 ERP recordings – the equipment

The technical equipment varies in different studies. Currently, specific nets with 128 (129, including a reference channel in the midline) electrodes are available. Some researchers in the audiological field use this type of net (Liang et al., 2014; Turgeon et al., 2014). Other options are 40-channel systems (Zhang et al., 2013) or 21 silver-silver chloride electrodes (Singh et al., 2004). However, even if plenty of channels are recorded, only a few are normally selected for further analyses.

2.2.1.4 *Electrophysiological processing and analyses of ERP data*

Some of the most important steps in the further processing of the ERP recordings include sampling, filtering, segmentation, and artefact correction, to mention. A detailed description is provided in *4.2.2.2 Electrophysiological processing and analyses of ERP data.*

2.2.1.5 *Artefacts*

The EEG signal can be contaminated by other signal sources, resulting in so called artefacts. Eye blink and movements are the two main sources of such interference in the EEG examination. CIs cause a large stimulation artefact, which must be removed. Today, independent component analysis (ICA) is normally used for this purpose (Gilley et al., 2006).

2.2.1.6 *Statistics*

For the statistical analyses, analysis of variance (ANOVA) models are the most appropriate for ERP recordings, for example, 1-way ANOVA (Liang et al., 2014; Sharma et al., 2002), 3x2x3 ANOVA (Turgeon et al., 2014) and repeated measures ANOVA (Zhang et al., 2013). Group average analyses are commonly used.

2.2.2 Mismatch negativity

Risto Näätänen, a Finnish cognitive neuroscientist, is one of the discoverers of MMN. MMN reflects the detection of minor differences in sound, which are important for the ability to understand speech. It is an automatic brain response to any discriminable change in auditory stimulation. It is regarded as a subconscious process not requiring active listening. A rare stimulus, or deviant, causes a stronger ERP response compared to a standard stimulus. MMN is calculated from the deviant ERP response minus the standard ERP response, thus forming a difference wave. (Naatanen et al., 1978).

Today, MMN is a well-established research method described in specific textbooks (Luck, 2014). Guidelines and recommended recording conditions for MMN are compiled (Duncan et al., 2009) along with practical toolkits (Dien, 2010). Nevertheless, various models are being used, including different approaches to analysis and interpretation of the results. For instance, there are variations regarding the handling of technical equipment, the characteristics of the stimuli, the ERP processing, including sampling, filtering, segmentation, and artefact correction, as well as the statistical analyses. Calculation of MMN itself implies some options. Peak or mean amplitude can be used, as well as latency or area under curve. MMN typically peaks between 160 and 220 ms (Luck, 2014) but other time periods can be chosen. Some MMN results are based on a subjective visual evaluation of the waves (Liang et al., 2014). The scalp distribution, also known as the topography (Ponton et al., 2000), of the MMN is another option.

2.2.2.1 *Stimuli and the Optimum-1 paradigm*

Different stimuli can be used in ERP recordings. MMN requires a standard stimulus as well as one (or more) deviant(s). The mismatch responses may be obtained differently by different stimuli (Cheour et al., 2000). The multi-feature paradigm, Optimum-1 (Naatanen et al., 2004), uses five different deviants: gap, intensity, pitch (or frequency), location, and duration. Optimum-1 is efficient, since it tests all deviants in the same session, enabling use with awake children (Putkinen et al., 2012) including children with HAs (Koravand & Jutras, 2013; Koravand et al., 2013). However, the stimuli characteristics may vary. Some researchers have exclusively chosen a few deviants, for example, frequency and duration (Lonka et al., 2013), or pitch (Zhang et al., 2013). The number of stimuli can vary, as well as the interstimulus interval (ISI). Moreover, MMN can also be elicited by different syllables (Getzmann & Naatanen, 2015). Other examples are a synthesised speech syllable /ba/ (Sharma et al., 2002) or /da/ and /ba/ versus /da/ and /ga/ (Turgeon et al., 2014). Even vowels seem to serve as stimuli in toddlers, as observed with one-year-old NH Finish children's increased MMN amplitudes with vowels in their native language compared to Estonian vowels (Cheour et al., 1998). When using speech phoneme as stimuli, school-age children present adult-like MMN with respect to peak latency, duration, and area (Kraus et al., 1993).

2.2.2.2 Mismatch negativity and positive mismatch response

One challenge with interpreting MMN is the maturational changes during life, affecting children in particular (Bishop et al., 2011; Cheour et al., 1998; Morr et al., 2002; Shafer et al., 2010). Researchers have observed changes in both amplitude and latency and have tried to outline the normal development from infancy and childhood (Bishop et al., 2011; Cheour et al., 1998; Morr et al., 2002; Shafer et al., 2010) to adolescence (Cooray et al., 2016). Even prenatal studies have been conducted (Draganova et al., 2005). Though, some results infer that MMN is quite stable during childhood (Cheour et al., 2000) after reaching an age of 5 years (Gomot et al., 2000). Under the age of 5.5 years, a positive mismatch response (pMMR) is observed (Shafer et al., 2010). The typical negative MMN is considered adult-like, whereas pMMR seems to reflect immaturity. A more mature discrimination process might mask the pMMR (Morr et al., 2002; Weber et al., 2004) and absence of MMN should not necessarily mean it does not exist. Rather, it may be hiding behind an overlapping pMMR (Shafer et al., 2010).

2.2.3 Event-related potentials and mismatch negativity in different clinical conditions including hearing loss

MMN is believed to be related to cognitive development, and, in recent decades, ERP and MMN have contributed to knowledge about different clinical conditions, including different neurodevelopmental, neuropsychiatric, and neurological disorders (Cheour et al., 2002; Guttorm et al., 2001; Hamalainen et al., 2007; Naatanen et al., 2012; Naatanen et al., 2015). Since MMN is considered to reflect discrimination ability, which is of importance for phonological processing skills, it makes MMN of special interest to study in developmental language disorders, dyslexia, and reading disorders (Guttorm et al., 2001; Huttunen et al., 2007), especially those pertinent to children. The use of MMN in this field was reviewed already in 1997 (Leppanen & Lyytinen, 1997). For example, children with reading disability have shown lateralisation of the MMN peak amplitudes (Huttunen et al., 2007).

ERP and MMN are also used to study the central auditory processing and development among patients with HL, especially patients with CIs (Bishop, 2007; Naatanen et al., 2017; Ponton et al., 2000). There are electrophysiological differences between patients with HL compared with NH persons (Sharma et al., 2002), including differences in MMN regarding children with HL (Koravand et al., 2013). Children with CI show different auditory evoked potentials compared to children with NH (Ponton et al., 1996; Ponton et al., 2000). It seems reasonable to assume that a pre- or post-lingual deafness might affect the ERP and MMN. MMN provides a neurophysiological measure and can also be used as a tool for an objective assessment of CI functioning after implantation and as a function of time of CI use (Naatanen et al., 2017). MMN helps to map the development of the central auditory pathways and the neuroplasticity of the brain and contributes to more information about differences between CI patients and NH persons (Sharma et al., 2002; Sharma et al., 2009).

Regarding MMN and HL, only a few studies include patients with HAs. Most studies are based on patients with HL using CI, specifically, and it must be emphasised that some of those refer to adults only, which means there are no interfering maturational changes to consider. The immediate and controlled shift from deafness to hearing after CI power-up makes CI patients appropriate in human models for research of the brain plasticity and neurophysiology overall. Though, it is important to account for the possible heterogeneity described above, see Section *2.1.3 Children with hearing loss*. Moreover, CIs generate artefacts in the ERP recordings, which increase the complexity of data processing.

Sharma et al. have published several more extensive studies, for example, 121 patients with CI and 136 persons with NH were reported in 2002 (Sharma et al.). MMN was not specifically analysed, but CAEP and latencies of P1. More than 100 children between approximately 2 years and 18 years old participated. The participants were divided into 3 groups depending on time for implantation (early/middle/late). Patients with congenital deafness and profound HL at the age of 1 year were grouped together. The results are clinically important, suggesting maximal plasticity in the human central auditory system up to 3.5 years, which support early implantation children with congenital deafness. On the contrary, after the age of 7 years, the plasticity seems to be greatly reduced. (Sharma et al., 2002). This might explain why children with congenital deafness seldom develop spoken language if implantation is performed after the age of 6–7 years. These results are consistent with results based on analysis of P1 latencies in 245 congenitally deaf children fitted with CI, where early implantation was followed by normalisation of P1 latencies (Gilley et al., 2006). Thus, in congenitally deaf children fitted with CIs, the first positive wave of CAEP, P1, is suggested as a neurophysiological marker for the development and reorganisation of the central auditory system (Sharma et al., 2009).

Studies observe prolonged MMN latency and reduced MMN amplitude in CI users compared to NH persons (Turgeon et al., 2014). However, this can be hard to statistically prove, and results are partly contradictory. Liang et al. found that the MMN latencies decreased in children between 3 and 6 months after implantation while there were no differences in the amplitudes during this period (Liang et al.). On the other hand, Turgeon et al. concluded that the amplitudes of MMN were significantly lower in CI users classified as poor performers on a speech recognition task, whereas the latency of the MMN seemed to be a less appropriate indicator for CI speech recognition (Turgeon et al., 2014). Another study showed that the MMN amplitudes increased over time after implantation, although the results varied between different deviants, for example, MMN was elicited by frequency but not duration (Lonka et al., 2013).

Another objective and non-invasive indicator for evaluating auditory central development, especially at an early stage after implantation, would be desirable. MMN might match this purpose, but further research is needed. In the longer term, this may be of importance and support the choice of intensified auditory rehabilitation (Liang et al., 2014).

MMN, elicited by non-speech or speech-like stimuli, is seen to be present among children with mild-to-moderate SNHL in the ages 8–11 years, but absent or even disappearing in children with HL in the ages of 12–16 years. Though, when using speech stimuli, MMN is consistent (Calcus et al., 2019).

2.2.4 Statistical analyses

Regarding the statistical analyses, ANOVA models are considered most appropriate in ERP studies and are commonly used for this purpose, for example, 1-way ANOVA (Liang et al., 2014; Sharma et al., 2002), 3x2x3 ANOVA (Turgeon et al., 2014) and repeated measurements ANOVA (Zhang et al., 2013). In addition, group average analyses or individually presented results (Liang et al., 2014) are two options.

2.3 COMPUTER-ASSISTED READING INTERVENTION (GRAPHOGAME)

Heikki Lyytinen at the University of Jyväskylä in collaboration with the Niilo Mäki Institute in Finland developed the computer-assisted reading intervention, GraphoGame (*Ekapeli* or *Spel-Ett*, in Finnish and Swedish, respectively) at the beginning of the 1990s. Briefly, the aim was to enhance the support of children with reading disabilities (Saine et al., 2011) and dyslexia (Lyytinen et al., 2015; Lyytinen et al., 2009). The Jyväskylä Longitudinal Study of Dyslexia comprises a series of developmental studies of brain responses, meaning different ERP studies. Above all, children with familial risk for dyslexia have been compared with children without any risk (Cheour et al., 2002; Guttorm et al., 2001; Hamalainen et al., 2007). ERP measures have also been used to predict later pre-reading and reading skills (Bach et al., 2013; Guttorm et al., 2010; Leppanen et al., 2010). This means ERP may at an early stage help to identify children at risk for developmental language problems. Changes in MMN have been seen after phonological training in NH adults (Kraus et al., 1995) as well as after audio-visual training in dyslexic children (Kujala, Karma, et al., 2001).

GraphoGame is designed for pre-school children and beginning readers and is thought to help children learn reading (Ojanen et al., 2015). GraphoGame starts with basic letters and their sounds, and gradually moves on to short and increasingly longer words. The difficulty level is individual and dynamically adapted to the ability level of each child. Phoneme-grapheme correspondence (the fundamental basis of reading skills) training is the main focus. Nowadays, the programme is established internationally, and it is also translated into other languages, including Swedish. Swedish is a Germanic language with some relationship between letters and sounds, but it is not as transparent as Finnish (Lyytinen et al., 2015). The Swedish version of GraphoGame is structured in 56 levels. GraphoGame is available on the internet, meaning the children can play GraphoGame at home. Repeated playing during short periods on a daily basis is recommended.

3 RESEARCH AIMS

The overall aim of this thesis was to gain knowledge about the central ability to hear and discriminate small changes in auditory stimulation among children with HL by recording ERP and MMN.

Paper I

The aim was to explore whether a multi-feature paradigm (Optimum-1) for eliciting MMN could characterise difficulties in perceiving small sound contrasts in children with HL using their HAs or CIs. Children with NH were tested as a reference group.

Paper II

The aim was to investigate whether a computer-assisted reading intervention programme with a phonics approach (GraphoGame) could affect ERP and MMN in children with HL using HAs. Children with NH were tested as a reference group.

Paper III

The aim was to investigate whether a computer-assisted reading intervention programme with a phonics approach (GraphoGame) could affect ERP and MMN in children with CIs. Children with NH were tested as a reference group.

Paper IV

The aim was to examine how ERP and MMN change and develop over time (three years) among children with HL using HAs or CIs. Children with NH were tested as a reference group.

4 MATERIALS AND METHODS

4.1 PARTICIPANTS

4.1.1 Eligibility and recruitment

Most of the children with HL were recruited from the Department of Hearing and Balance/ENT at Karolinska University hospital, and a few patients from the hospitals in Lund and Uppsala. The children with NH were recruited from preschools and schools in Stockholm and Uppsala. From the beginning, the study group was small - only 80 children met the inclusion criteria. *Figure 3* provides a study flow chart over the selection procedure.

The participating children, referring to the children with HL and the children with NH, were approximately 5–8 years old at baseline (the first ERP recording session; ERP 1), versus 8–11 years old at the follow-up after three years (the third ERP recording session; ERP 3), see *Table 3*. One of the inclusion criteria was the age span 5–7 years, however, due to the timeline of the selection procedure and the ERP recordings, one child with NH had passed the age of 7. Furthermore, due to scheduling agreements at the request of participating families, two of the children with CIs did accomplish the first ERP recording (ERP 1) just before reaching the age of 5 years (4 years, 10 months and 16 days vs 4 years, 11 months and 24 days).

Children with other diseases or disabilities affecting speech and language development were removed from the participant selection. Additionally, due to the phonological approach utilised for the intervention stage, children who were not native Swedish speakers were not invited.

Four of the participating children were excluded due to ERP registration failure, for not matching the inclusion criteria (additional information from the parents after inclusion), or for not completing the intervention. In summary, there were three equally sized groups: the NH group (16 children in **Paper I**; 14 children in **Paper II** and **III**), the HA group (15 children), and the CI group (15 children; 9 children with bilateral CIs and 6 children with a combination of CI and HA). For the follow-up study (**Paper IV**), there was a dropout of 8 children with HAs, 9 children with CIs or HA/CI and 4 children with NH, resulting in three groups: NH group (10 children), HA group (7 children), and CI group (6 children; 5 children with bilateral CIs and 1 child with a combination of CI and HA).

All children with HL were using bilateral devices; bilateral HAs or bilateral CIs. A subgroup of children combined HA with CI and was studied together with the children with bilateral CIs, since the HL was severe to profound on the remaining hearing ear, and they relied mainly on their CI. The HL was SNHL, likely caused by a cochlear disorder since no medical records indicated ANSD. However, ABR testing was generally not performed to assess nerve functioning. Hearing among the children with NH was tested through the ordinary Swedish hearing screening programme at the Child Welfare Centres and School Health Service. Among the children with NH, 7 were siblings to the children with HL; however, one of them was excluded, and another sibling did not finish the intervention part.

All families were informed about the study both in writing and verbally. Two evening meetings were also held to provide information to the parents or guardians of the children, during which the parents or guardians had opportunities to ask questions about the project. Each child was individually and verbally informed about the study prior to the testing sessions. Parental informed consent was obtained from all participants. The project was approved by the Regional Committee for Medical Research Ethics in Stockholm, Sweden.

Due to confidentiality requirements and in line with the requests of the patients, certain information was omitted in some tables. No data relevant for the results was removed.

Table 3. *Ages* in the participating children, study I–IV.*

	NH group	HA group	CI group
Paper I (ERP 1) n=46	5y01m–8y01m n=16 (5 girls)	5y00m–7y08m n=15 (9 girls)	4y10m–7y8m n=15 (9 girls)
Paper II (ERP 1) n=29	5y01m–8y01m n=14 (4 girls)	5y00m–7y08m n=15 (9 girls)	-
Paper III (ERP 1) n=29	5y01m–8y01m n=14 (4 girls)	-	4y10m–7y8m n=15 (9 girls)
Paper IV (ERP 1) n=23	5y11m–8y01m n=10 (3 girls)	5y01m–7y08m n=7 (5 girls)	4y11m–6y10m n=6 (4 girls)
Paper IV (ERP 3) n=23	8y10m–11y00m n=10 (3 girls)	7y6m–11y0m n=7 (5 girls)	8y4m–9y10m n=6 (4 girls)

ERP, event-related potential; NH, normal hearing; HA hearing aid; CI, cochlear implant; y, year; m, month.
**In Paper I, values (ages) are rounded, for example, the age '7 years 11 months and 30 days' (example referring to control number 14, table 2, Paper I) is rounded to 8 years and 0 months; in Paper II–IV, ages are based on whole years and whole months, thus, the same example: 7 years and 11 months. (Table by Elisabet Engström.)*

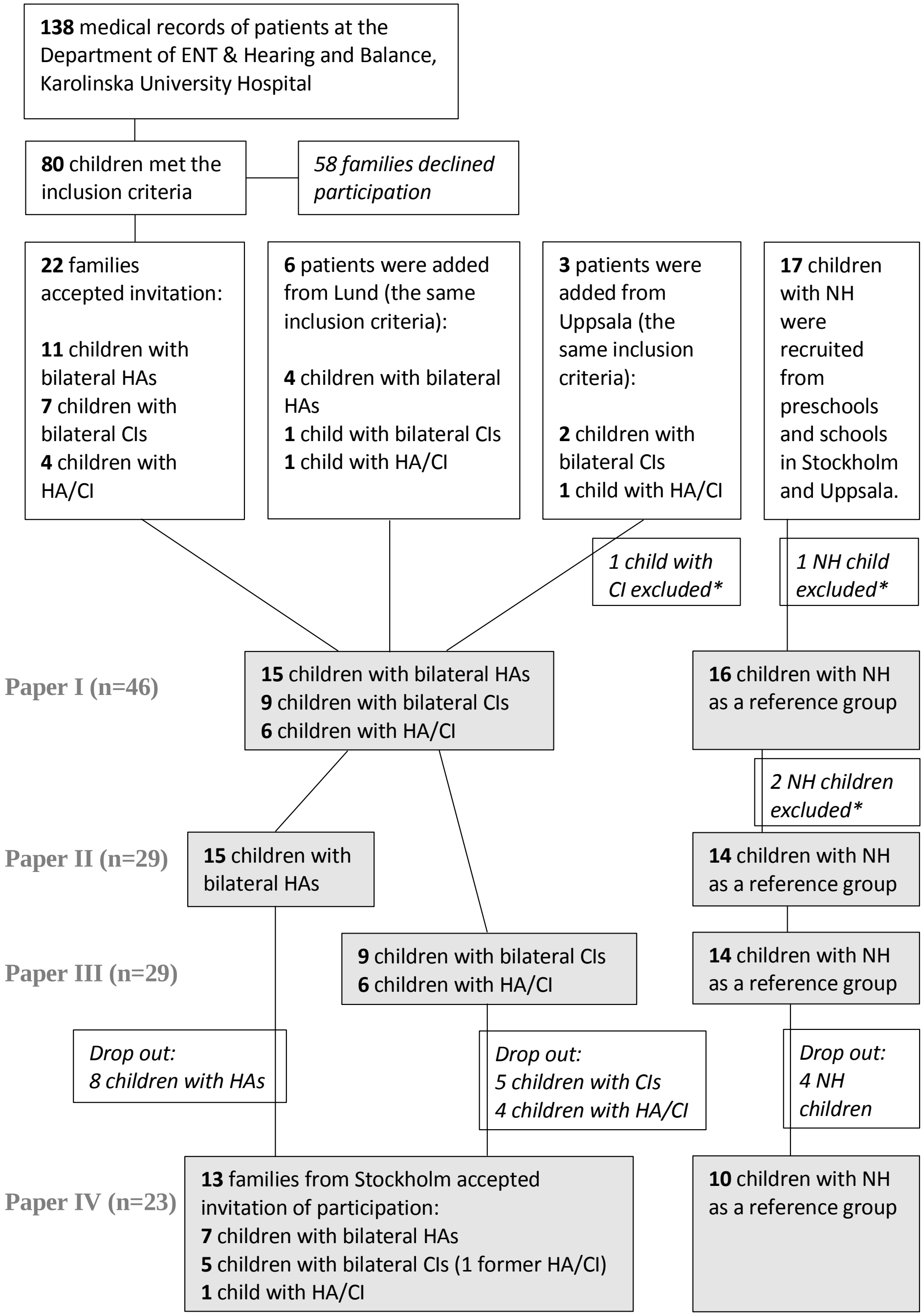


Figure 3. *Study flow chart of children with hearing loss (HL) and the reference group in all studies (study I–IV). HA, hearing aid; CI, cochlear implant; NH, normal hearing. *Exclusion due ERP registration failure, not matching the inclusion criteria, or not finishing the intervention. (By Elisabet Engström.)*

4.1.2 Hearing data

Medical records were studied regarding hearing data and patient history. However, OAE testing in new-borns was not yet part of the national hearing screening programme in Sweden, when the eldest of the participating children were born. Only a few of the children with HL had undergone the OAE testing in the neonatal period. ABR results were available from the neonatal period in a few cases.

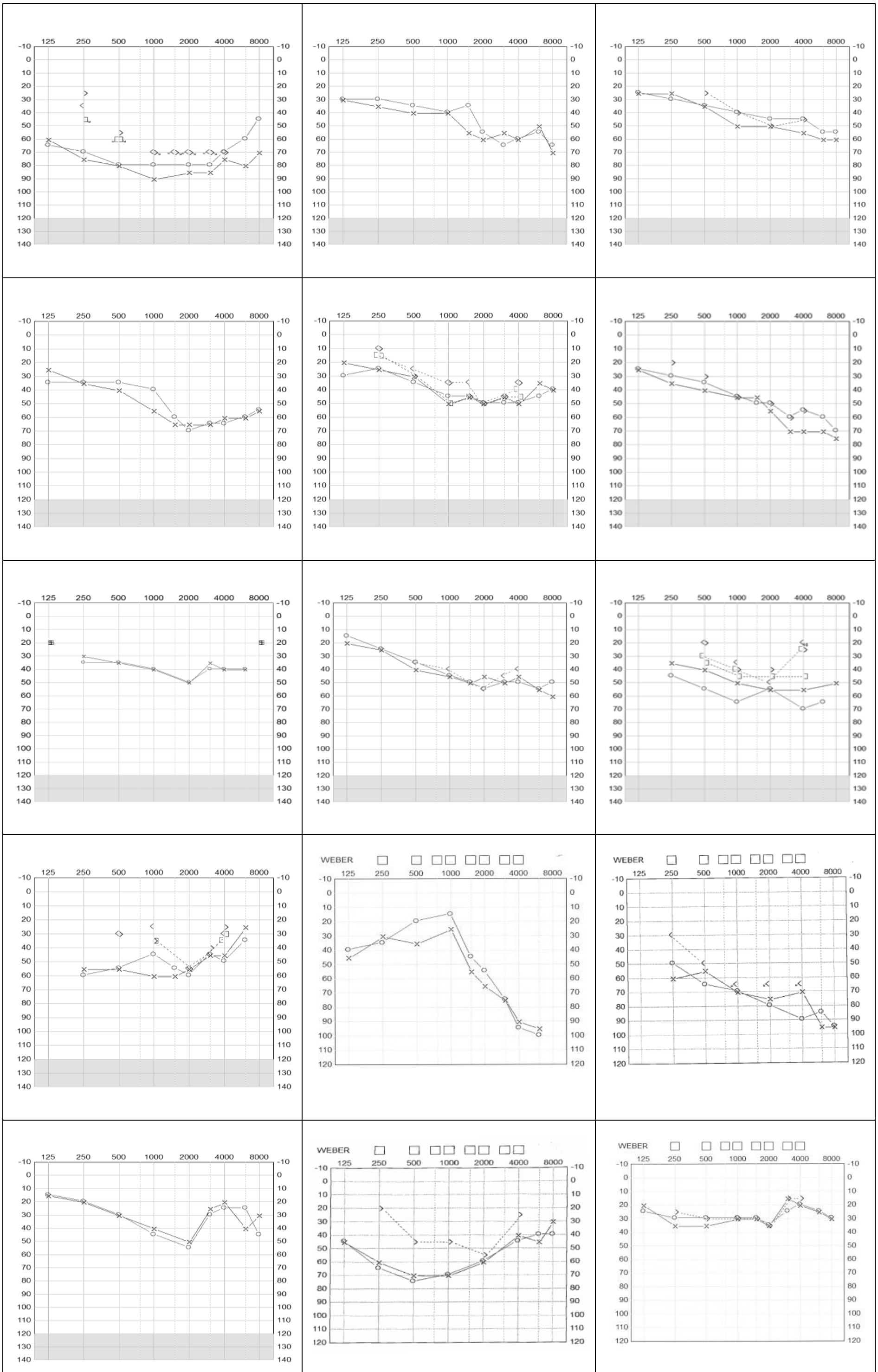
Beyond PTA, all patient audiograms were visually evaluated regarding the shape consistent with a mid- or high-frequency HL. The affected frequencies reflect some of the difficulties a child with HL might have, for example, high frequencies cover some of the important voiceless plosives and fricatives in Swedish spoken language. Visually, a u-shape HL (mid-frequency HL, or so called ‘cookie bite HL’) was seen or subtly indicated in 9 patients. A high-frequency HL (‘ski-slope curve’) down to approximately 60 dB hearing level or more was seen in 6 patients, including 1 boy who previously had received ototoxic drugs and in 2 children with a known mutation of the connexin 26 gene. However, subjective evaluations of audiograms can be difficult and challenging, and this kind of ‘classification’ must be interpreted with caution. For an illustration and transparency, the individual audiograms from the children with HAs (n=15) are presented in *Figure 4.* The audiograms refer to the hearing thresholds at baseline.

The children with HA were using digital devices from either Phonak™ (Stäfa, Switzerland) or Oticon™ (Copenhagen, Denmark).

The CI programming was performed individually for each patient, around a hearing level around 30 dB. The hearing thresholds in the children with hearing in one ear were 59–101 dB at baseline. At follow-up, two of these children had received bilateral CI; however, only one of them accepted participation at the three-year follow-up. Thus, at follow-up (**Paper IV**), only one child with a combination of HA/CI participated. The PTA4 on the remaining ear was in this child 80 dB.

The children with CI were using implants from either MED-EL™ (Innsbruck, Austria) or Cochlear™ (Australia).

Figure 4 (next page). *Audiograms from the children with bilateral hearing aids (n=15), at baseline. Air conduction right ear is marked with O; left ear is marked with X. X-axis: frequency, hertz (Hz); Y-axis: dB hearing level. Due to confidentiality requirements, all subject numbers are removed. (By Elisabet Engström.)*



125 250 500 1000 2000 4000 8000
-10 0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
WEBER

4.2 METHODS

4.2.1 Design of the project

All studies (**Paper I–IV**) are based on ERP recordings, as fully described below. The design is partly experimental. **Paper I** includes all participants at baseline. **Paper II** (children with HAs) and **Paper III** (children with CIs) involve the intervention part and two ERP recording sessions. **Paper II and III** separate the children with HAs from those with CIs, to better clarify the existing differences in these subgroups of children with different degrees of HL and type of hearing devices. Furthermore, the studies were subjects to an extensive evaluation procedure, due to the repeated ERPs, and the intervention part. Processing of the data from the children with CI also needed an additional procedure removing the specific CI artefacts. **Paper IV** comprises the follow-up study after three years and includes all 3 groups; the children using HAs versus CIs, and the children with NH. For an overview of the design, see *Figure 5*.

As there were a limited number of children with HL, and as all families specifically requested the intervention, the intervention parts (**Paper II and III**) were designed with an NH age-matched reference group with training, instead of utilising a group without training.

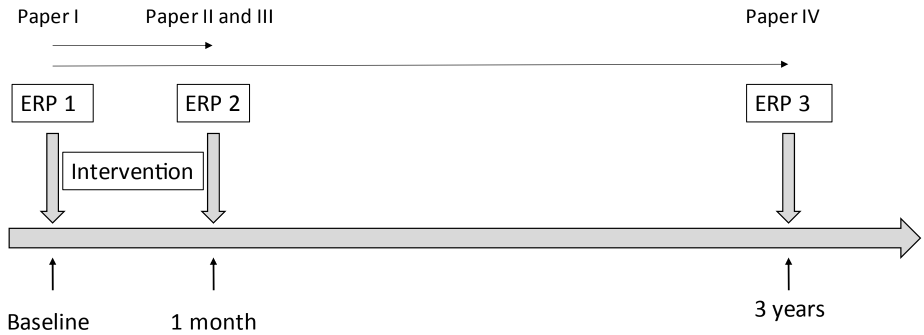


Figure 5. *Timeline, all papers (I–IV). Paper I includes all participants (three groups: children with hearing aids, cochlear implants vs normal hearing) at baseline. Paper II (children with hearing aids vs normal hearing) and Paper III (children with cochlear implants vs normal hearing) involve the intervention part and two ERP recording sessions. Paper IV comprises the follow-up study after three years (all three groups). (Illustration by Elisabet Engström.)*

4.2.2 Electrophysiological recordings

Most of the ERP recordings were performed at the Phonetics Laboratory at the Department of Linguistics, Stockholm University. The electrophysiological cortical responses were digitally recorded using HydroCel Geodesic Sensor Net (Net Amp 300, Electrical Geodesics Inc., Eugene, OR, USA) with 129 electrodes, including a central electrode in the midline (Cz; central zero) as a reference channel. Different sizes of the net were available for better fit among the children. The horizontal and suborbital electro-oculograms (EOGs) were removed in the smallest net sizes, leaving 125 channels. Another 6 children with HL were tested at the Humanities Laboratory, Lund University, due to logistical difficulties following large distance between the cities. The same type of equipment was used in both laboratories, and the testing procedure was equivalent.

In total, three ERP recordings were completed: ERP 1 at baseline; ERP 2 after the intervention; and ERP 3 as a 3-year follow-up.

4.2.2.1 Stimuli

Time and effort were spent enhancing the general testing conditions, in order to create an environment suitable for children in the current age range, since data with as few movement artefacts as possible is of the essence. Therefore, testing adults with NH and HL, as well as children with NH, preceded the studies. This promoted shorter test sessions (12 minutes instead of 15), and due to the hearing devices, the stimuli had to be presented through loudspeakers and not via headphones. These were placed in front of the child, 45° on each side, 70 dB hearing level. Otherwise, the multi-feature paradigm, Optimum-1, designed by Näätänen (Naatanen et al., 2004) was emulated. Thus, a standard stimulus alternated with five different deviants (gap, intensity, pitch, location, and duration), see *Table 4*. The stimuli were presented in a pseudorandom sequence, and every second stimulus was a deviant. There were around 120 stimuli of each deviant.

Table 4. *Stimuli characteristics: standard stimulus compared to the deviants.*

Stimuli	Standard	Deviant
Frequency	Harmonic tones; 3 sinusoidal partials of 500, 1000 and 1500 Hz	10% higher; 550, 1100, 1650 Hz (half of each) or 10% lower; 450, 900, 1350 Hz (half of each)
Duration	75 ms, including 5 ms rise and fall times	25 ms
Intensity	2nd partial 3 dB lower; 3rd partial 6 dB lower	10 dB higher or 10 dB lower, half of each
Location*	Equal right and left side	Interaural time difference of 800 μs to the right or left side, half of each.
Gap	None	7 ms (including 1 ms fall and rise times) silent gap in the middle of the tone

** A change in the perceived sound-source location between the standard stimulus and the location deviant was approximately 90°. Table from Paper II, (Engstrom et al., 2019). 2018 by Elsevier B.V. Reprinted with permission.*

4.2.2.2 Electrophysiological processing and analyses of ERP data

Data was pre-processed, including sampling, filtering, segmentation, and artefact correction. The EP Toolkit (Dien, 2010) was used for the automatic pre-processing. EP Toolkit runs in MATLAB® and offers software tools for analysis of ERP data. It is a toolkit for all aspects of EEG/ERP analysis, especially principal component analysis (PCA). The specific CI artefacts were treated with an additional ICA-based procedure in EEG Lab (Delorme & Makeig, 2004; Jung et al., 2000).

The ERPs from the standard stimulus and the five deviants underwent averaging procedures, creating subject average files. MMN was calculated from each deviant average ERP minus standard average ERP. For the further statistical analyses, seven fronto-central channels between the frontal electrode in the midline (Fz; frontal zero) and Cz were selected. The largest responses were assumed to be obtained in this area, according to prior studies (Duncan et al., 2009), and after evaluation of the ERPs in **Paper I**. Furthermore, time intervals based on visual inspection (**Paper I**) were chosen for the statistical analyses.

For an overview of the steps in the processing of the ERP data, see *Table 5*.

With the EP Toolkit, it is also possible to perform quality controls and view data as waveforms, for an illustration, see *Figure 6*. The settings can be changed manually. For example, it is possible to select individual patients, separate deviants, or create groups and an average of deviants. A few different curves can be selected in each view. *Figure 7* shows waveforms originating from EP Toolkit and provides a summary of the ERP and MMN of all patients (children with HA, CI, and NH; n=46).

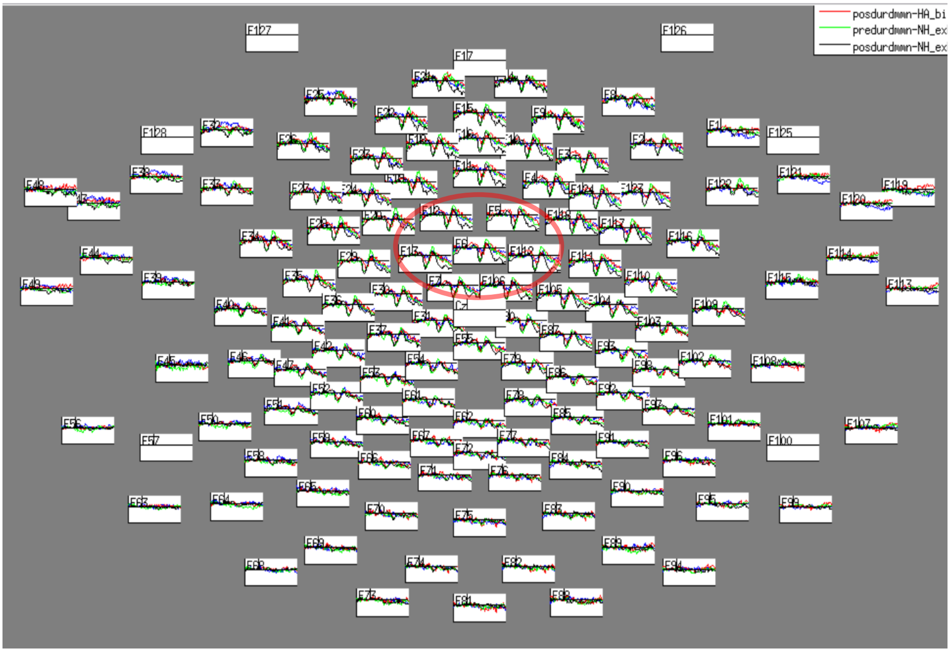


Figure 6. *Screenshot from EP Toolkit/MATLAB® showing the waveforms from all electrodes (HydroCel Geodesic Sensor Net); the duration deviant and children with hearing aids (HAs) and normal hearing (NH), are here used as an example for illustration. The red circle marks the seven selected fronto-central electrodes. (By Elisabet Engström.)*

***Table 5.** Summary of the ERP processing.*

Step	**Comment**
Sampling	20 000 Hz
Low pass filtering online	4 000 Hz
Resampling	250 Hz
Bandpass FIR (finite impulse response) filtering offline	1–40 Hz
Resampling of continuous data files	125 Hz
Epoching	100 ms before the event through 500 ms after, and baseline adjusted to 100 ms before onset of each stimuli
Rejection	Epochs with amplitudes exceeding ±500 µV
Exclusion of bad channels	Absolute correlation with neighbouring channels falling below 0.4
Detection and deletion of artefacts	Blink correction; independent component analysis (ICA) in comparison to a topographic blink template CI artefact correction; additional ICA-based procedure. Components were rejected in an iterative manner, reducing the CI artefact. Movement artefact removal; principal component analysis (PCA). Principal components >200 µV in amplitude changes caused removal.
Rejection	Epochs with amplitude differences >300 µV and with ≥25% bad channels were rejected.
Replacing	Bad channels were replaced via interpolation from the remaining good channels.
Re-referencing	ERPs were re-referenced to linked mastoids and baseline adjusted to 100 ms before onset of each stimuli.
Creating subject average files	ERPs from all stimuli, standard and all deviants
Calculation of MMN	Each deviant average ERP minus standard average ERP
Selection of electrodes for the statistics	Fronto-central electrodes; number 6, 5, 7, 12, 13, 106 and 112
Selection of time interval	For example, samples within 80–224 ms (Paper II–IV)

(Table compiled by Elisabet Engström.)

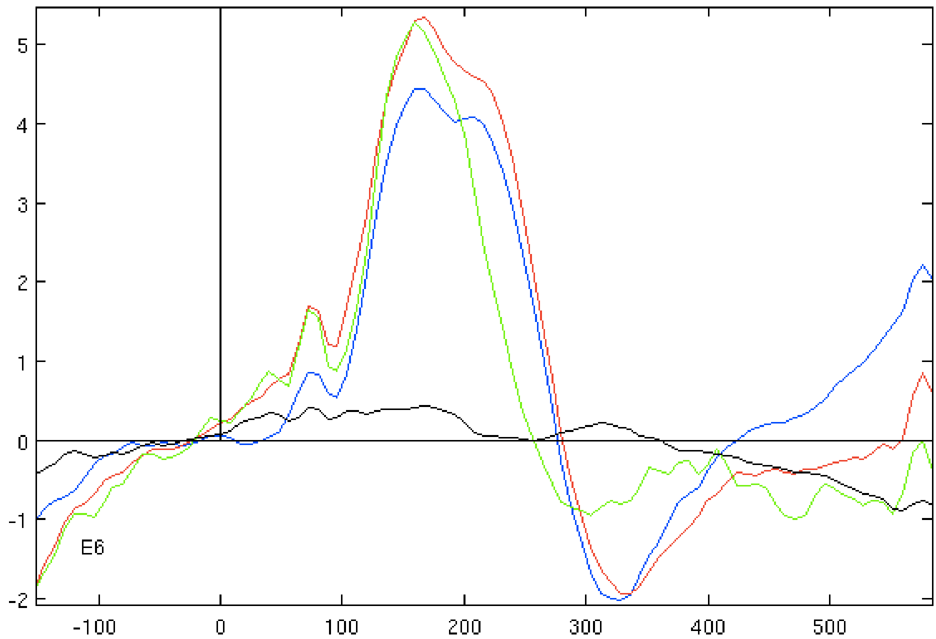


Figure 7. *Raw data for an illustration; gathered average from EP Toolkit/MATLAB®; ERPs and MMN of all participating children (n=46) at baseline (ERP 1), electrode number 6. Blue line: ERP of standard stimulus; red line: ERP based of all deviants but duration (gap, intensity, pitch, location); green line: ERP of duration deviant; black line: MMN of all deviants but duration. X axis: time (ms); Y axis: amplitude (µV). (By Petter Kallioinen, co-author of Paper I–IV.)*

The individual waveforms formed the starting point for interpretations and further analyses. For transparency and understanding of the underlying work, *Figures 8–10* display the individual waveforms: *Figure 8* concerns the children with NH; *Figure 9* the children with HAs; and *Figure 10* the children with CIs, where the interference of the CIs also can be descried. Since there was a visual similarity of the gap, intensity, pitch, and location deviants, they were gathered in EP Toolkit for the visual inspection. However, statistically, each deviant was separately analysed, and the results of ERP and MMN are presented on group level (HA, CI vs NH).

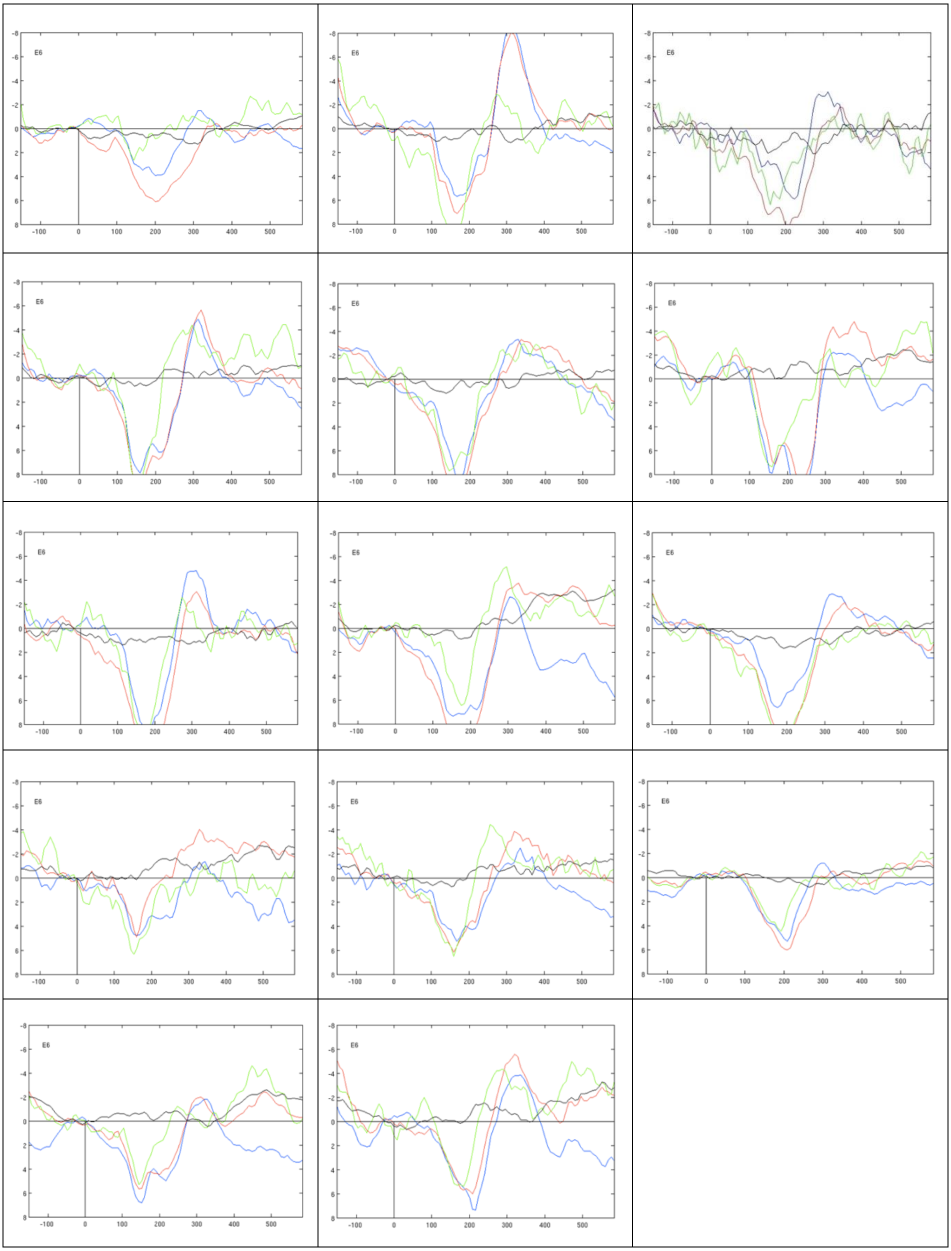


Figure 8. *Raw data; waveforms from EP Toolkit/MATLAB®. Individual ERP and MMN of the children with normal hearing (n=14; meaning the children with NH also participating in study II and III) at baseline (ERP 1). Blue line: ERP of standard stimulus; red line: ERP based of all deviants but duration (gap, intensity, pitch, location); green line: ERP of duration deviant; black line: MMN of all deviants but duration.*

X axis: time (ms); Y axis: amplitude (µV), negative values are towards the top of the figures. Due to confidentiality requirements, all subject numbers are removed. (Individual ERPs and MMNs by Petter Kallioinen, co-author of Paper I–IV.)

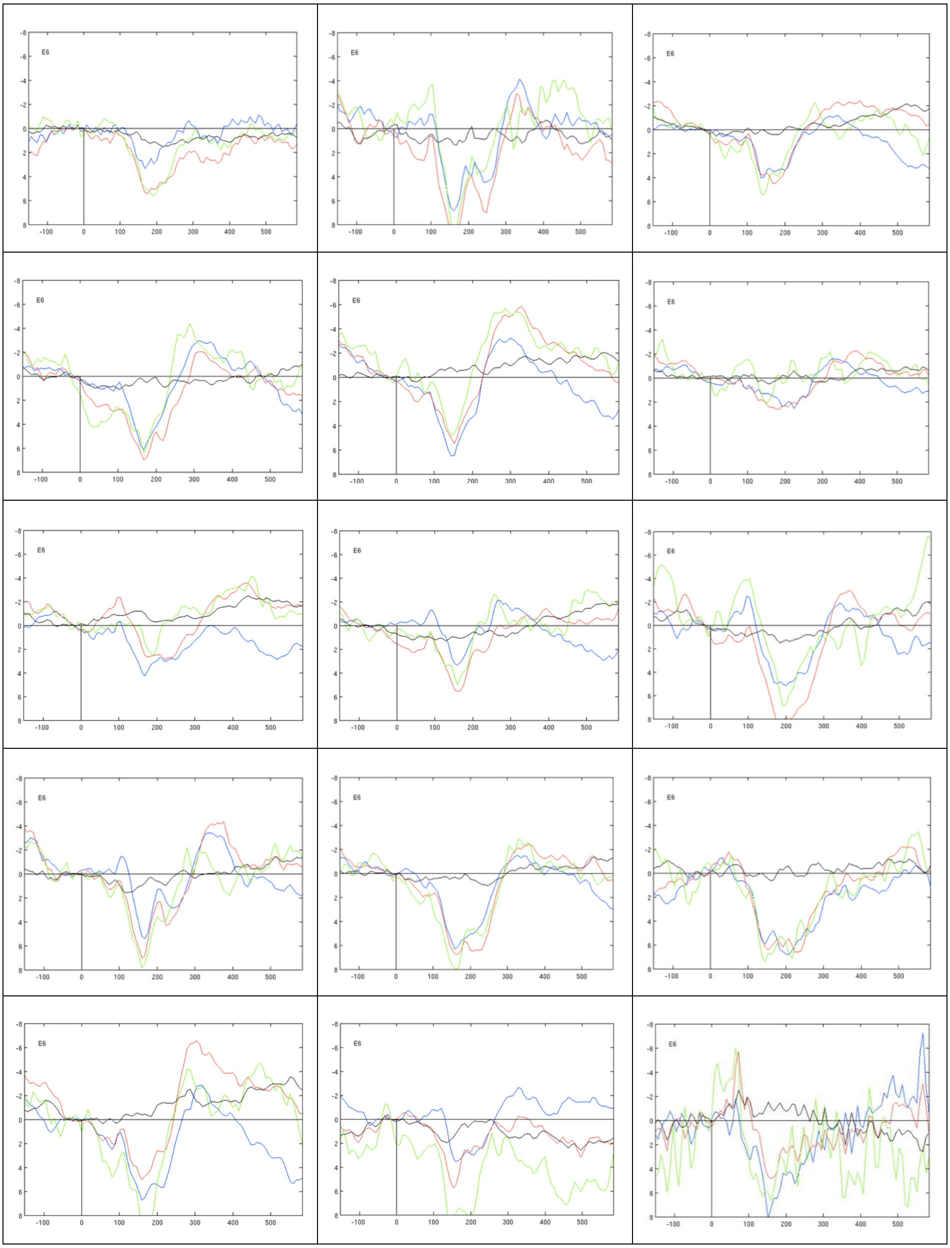


Figure 9. *Raw data; waveforms from EP Toolkit/MATLAB®. Individual ERP and MMN of the children with hearing aids (n=15) at baseline (ERP 1). Blue line: ERP of standard stimulus; red line: ERP based of all deviants but duration (gap, intensity, pitch, location); green line: ERP of duration deviant; black line: MMN of all deviants but duration.*

X axis: time (ms); Y axis: amplitude (µV), negative values are towards the top of the figures. Due to confidentiality requirements, all subject numbers are removed. (Individual ERPs and MMNs by Petter Kallioinen, co-author of Paper I–IV.)

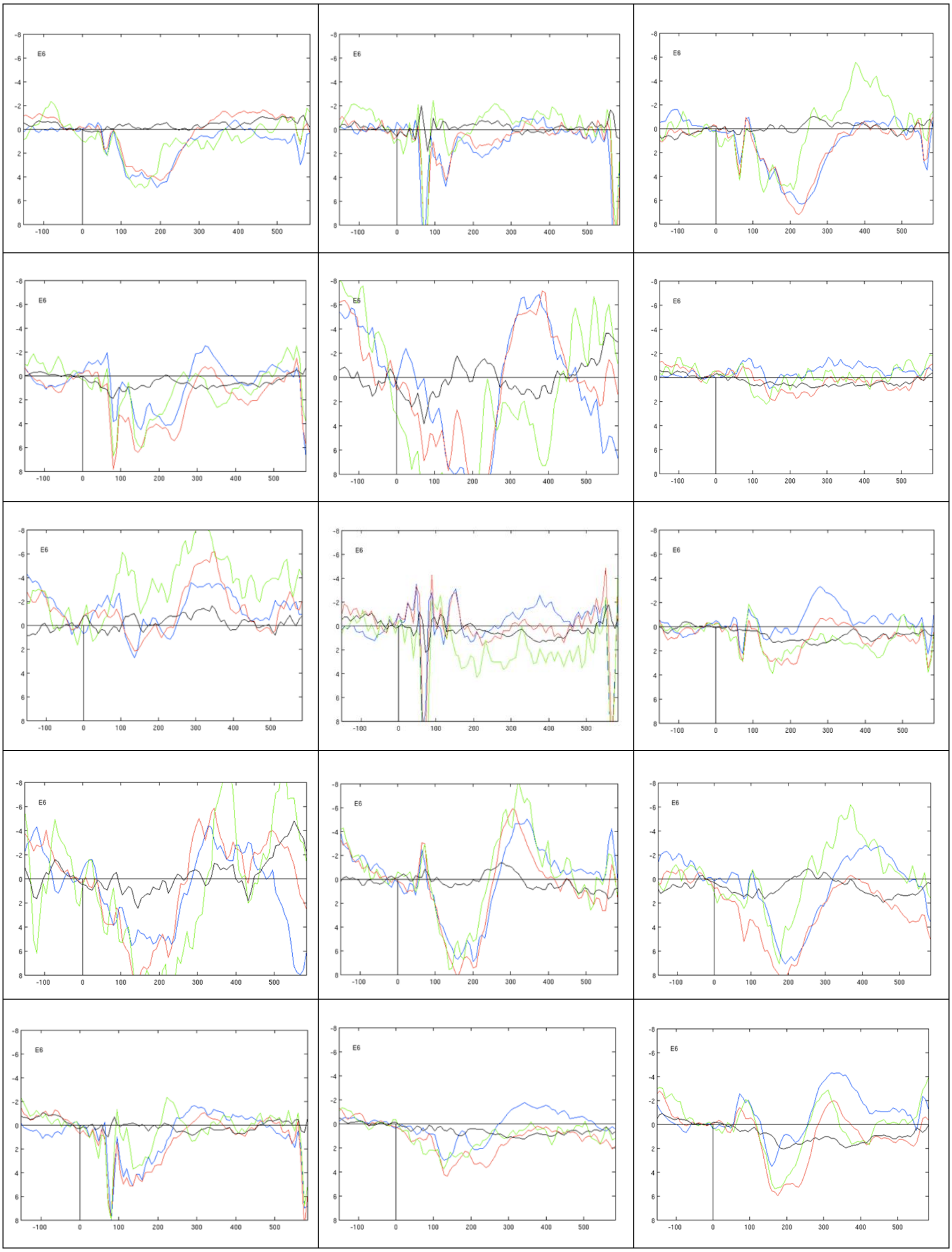


Figure 10. *Raw data; waveforms from EP Toolkit/MATLAB®. Individual ERP and MMN of the children with cochlear implants or combination of hearing aid and cochlear implant (n=15) at baseline (ERP 1). Blue line: ERP of standard stimulus; red line: ERP based of all deviants but duration (gap, intensity, pitch, location); green line: ERP of duration deviant; black line: MMN of all deviants but duration.*

X axis: time (ms); Y axis: amplitude (µV), negative values are towards the top of the figures. Due to confidentiality requirements, all subject numbers are removed. (Individual ERPs and MMNs by Petter Kallioinen, co-author of Paper I–IV.)

4.2.3 Intervention (GraphoGame)

The computer-assisted reading intervention programme with phonics approach constituted the intervention part. The children were asked to practice ten minutes per day at home during a period of 4 weeks, for an illustration, see *Figure 11*. Increased training was added other days if time was missing. The children with HL were using their devices; the HAs or CIs. They listened through external loudspeakers or a hearing loop, depending on how they normally used their computers. If needed, families were guided and supported by a speech pathologist in the research group.

Figure 11. *Children with hearing aids playing GraphoGame at home. Fictional patients; GraphoGame is meant for individual use. (Photo with permission from the children and their parents, by Elisabet Engström)*

4.2.4 Statistical analyses

The statistical analyses were performed in IBM SPSS® Statistics version 23.0.0.3. Repeated measures ANOVA was used since it is the model commonly used in ERP studies. ANOVA is appropriate due to the experimental design, the individuality of ERP and MMN, and the various factors.

Looking at **Paper II** as a model, there were 2 between-subject factors (the 2 groups: HA vs NH). Within-subject factors were time (before and after training, thus, 2 levels), and the 5 deviants. Hence, this formed a 2x2x5 ANOVA.

Thus, a three-way interaction in this illustration implied interaction between type of (one, or more) deviant(s), training and whether HA or NH. If no three-way interaction was found, the analyses proceeded with a two-way mixed ANOVA (HA vs NH as between-subject factors) and deviants or time as the within-subject factors. The primary goal of running a two-way mixed ANOVA was to determine whether there was a two-way interaction between the between- and within-subject factors (meaning a group x time interaction). When having a statistically significant interaction, the main effects for the between- and within-subject factors must be interpreted, to inform where the differences in ERP or MMN response between time points or groups lie. In other words, a two-way interaction could show interactions between groups before or after training, see *Figure 12*, or changes over time within each group, see *Figure 13*. Both figures are here only used as example models.

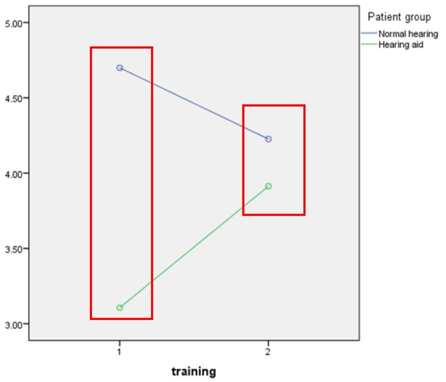


Figure 12. *Testing for the simple main effects for group, that is, differences in mean ERP response between groups at each category of the within-subject factor: time. The illustration refers to mean ERPs (mean amplitude of the obligatory responses, all deviants and standard before (1) and after (2) training in the hearing aid (blue line) and normal hearing (green line) groups. Figure adapted from Paper II, (Engstrom et al., 2019). 2018 by Elsevier B.V. Reprinted with permission.*

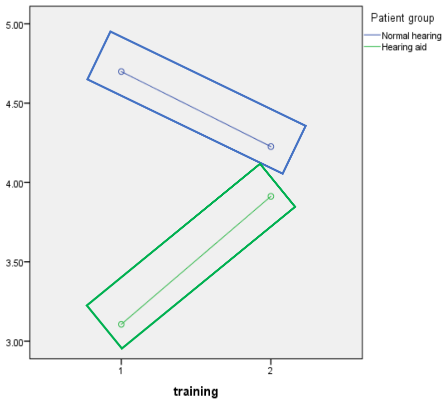


Figure 13. *Testing for the simple main effects for time means testing for differences in ERP response between time points for each category of the between-subject factor: group. The illustration refers to mean ERPs (mean amplitude of the obligatory responses, all deviants and standard before (1) and after (2) training in the hearing aid (blue line) and normal hearing (green line) groups. Figure adapted from Paper II, (Engstrom et al., 2019). 2018 by Elsevier B.V. Reprinted with permission.*

4.3 ETHICAL CONSIDERATIONS

The most important ethical considerations concern the participants being children. However, any research involving patients with HL also warrants reflections and considerations.

4.3.1 Participants

Most of the children with HL were recruited from the Department of Audiology and Neurotology at Karolinska University Hospital. The study group was limited from the start, only 80 of 138 children (58%) at Karolinska University Hospital met the inclusion criteria. Children with other diseases or disabilities that might affect speech and language development were removed from the inclusion criteria. Additionally, due to the phonological approach utilised in the intervention stage, children who were not native Swedish speakers were also excluded.

Children with CIs (and their parents or guardians) have shown a high degree of interest in participating in relevant studies, and several research projects have been undertaken involving this subgroup of children with HL. Accordingly, it is possible that many of these same children may have participated in other studies, resulting in them becoming overtired of, or overly familiarised with, professional testing situations.

All families were informed about the study both in writing and verbally. Two evening meetings were also held to provide information to the parents or guardians of the children, during which the parents or guardians had opportunities to ask questions about the project. Each child was individually and verbally informed about the study prior to its start date.

Children with HL, and their parents or guardians, frequently visit health care and habilitation centres, causing considerable time away from school and work, respectively. The present studies were likewise time-consuming for the families. In Stockholm, all ERP recordings were performed at the Phonetics Laboratory at the Department of Linguistics at Stockholm University. This project, thus, focusing on electrophysiological recordings in children with HAs and CIs, was part of a more comprehensive project, which also included behavioural effects and phonological processing skills as well. Together, this resulted in between 2.5 and 3 hours of testing during each session, including breaks, with three sessions in total.

There was a substantial decrease in participation during the third-year follow-up. One reason may be the lack of time to participate in the study. Alternatively, as the children got older, their participation could have varied based on their own desires, rather than those of the parents. Furthermore, wearing HAs and CIs may be stigmatising, and some children may have wanted to avoid devoting significant attention to their condition. To help combat this trend, and to facilitate participation, test sessions were offered during the weekends.

The parents did not receive any compensation in return for participation in the study. However, the children were given a cinema ticket and an honorary diploma. During the breaks between the different testing sessions, they also were given something to drink and eat.

4.3.2 Design of the project

As there were a limited number of children with HL, and as all families specifically requested the intervention, the study was designed with an age-matched NH reference group with training, instead of the utilising a group without training. It was considered unethical to withhold the training programme from any of the children.

4.3.3 The method

The ERP recordings are non-invasive and safe. The largest inconvenience is that the hair gets wet during the net application and that the recordings are time-consuming and might be boring. Therefore, an effort was spent enhancing the general testing conditions for those participating in the study. This is especially important when testing children in the subject age range. For example, the children were seated in a comfortable chair, which could be individually adjusted; they were allowed to watch an animated movie without sound, and meal breaks were included. Additionally, the children were seated in a sound booth equipped with a speaker and a large window; recordings were cut off when needed, and pilot testing prior to the project reduced the total recording time by a few (3) minutes.

Applying the electrode net is itself time-consuming, taking around 10 to 15 minutes because all 129 electrodes must establish contact with the scalp. During this procedure, the children could not wear their hearing devices. Therefore, the children may have felt exposed and vulnerable, particularly the children with CIs. Communication was facilitated by talking louder and more slowly to the children with HAs. Lip reading or supporting hand-signs were used as a complement if needed. The parents stood close and could also support communication. The hearing devices were replaced as soon as possible. The children were also able to watch a movie in this part of the testing session.

Most children accepted to sit by themselves in the sound booth, although in some cases their parents joined them. Compared to those with NH controls, many of the children with HL were used to sit alone in this type of room from former experiences involving hearing testing. The children could see their parents through a window, and it was also possible to communicate through a speaker.

4.3.4 Performance of tests

MMN is an automatic brain response and does not depend on attention. Thus, testing MMN does not require any performance testing.

4.3.5 Intervention

Playing GraphoGame should have no negative side effects, and only a short (ten minutes) daily practise was required during the intervention month. Several children reached the maximum level, and after a month, some children reported they were bored.

4.3.6 Presenting data

Due to confidentiality requirements and in line with the requests of the patients, certain information is omitted in some tables (for example, family history and heredity in Appendix A, **Paper II**). No data relevant to the results was removed.

4.3.7 Ethical approvals

Ethical approvals were obtained by the Regional Committee for Medical Research Ethics in Stockholm, Sweden. All research was conducted according to the Helsinki declaration.

5 RESULTS

Since this thesis synthesises multiple works, there are additional, unpublished figures presented below. These figures provide further understanding of the analyses and interpretations of the results.

5.1 PAPER I

The purpose of this study was to investigate if ERP recordings and MMN could demonstrate altered, or absent, responses in basic features of speech, such as small contrasts in gap, intensity, pitch, location, and duration, in children with HL compared to children with NH. This paper considers how to analyse and interpret the results in current patient groups, including the selection of electrodes and varying time windows (TWs), based on visual inspection of all individual waveforms. A distinct negative peak for the MMN difference wave was not observed, resulting in the choice of mean amplitude for the further analyses. The paper constitutes a baseline and offers a description of the obligatory responses in ERP, the results of the different deviants, as well as MMN and pMMR.

In total, 30 children with HL using HAs (n=15) or CIs (n=15) participated, as well as 16 children with NH as a reference group.

The multi-feature paradigm, Optimum-1 (Naatanen et al., 2004), measuring five deviants (gap, intensity, pitch, location, duration) and a standard stimulus, was used for eliciting ERP.

The analyses of ERP and MMN are performed with comparisons between the children in the three groups (NH, HA vs CI) and each deviant is separately analysed as well. **Paper I** provides the structure for the analyses and models in the following **Paper II–IV**.

5.1.1 Electrode selection

Grand average ERPs for all electrodes, with mastoid reference, are shown in *Figure 14.* ERPs were similar across the scalp and showed maximal amplitudes at the fronto-central sites, which is typical with a mastoid reference and in line with earlier findings (Duncan et al.). Therefore, a group of seven fronto-central electrodes between Fz and Cz was chosen and used for all further analysis: channel E6 and the surrounding channels E5, E112, E106, E7, E13 and E12.

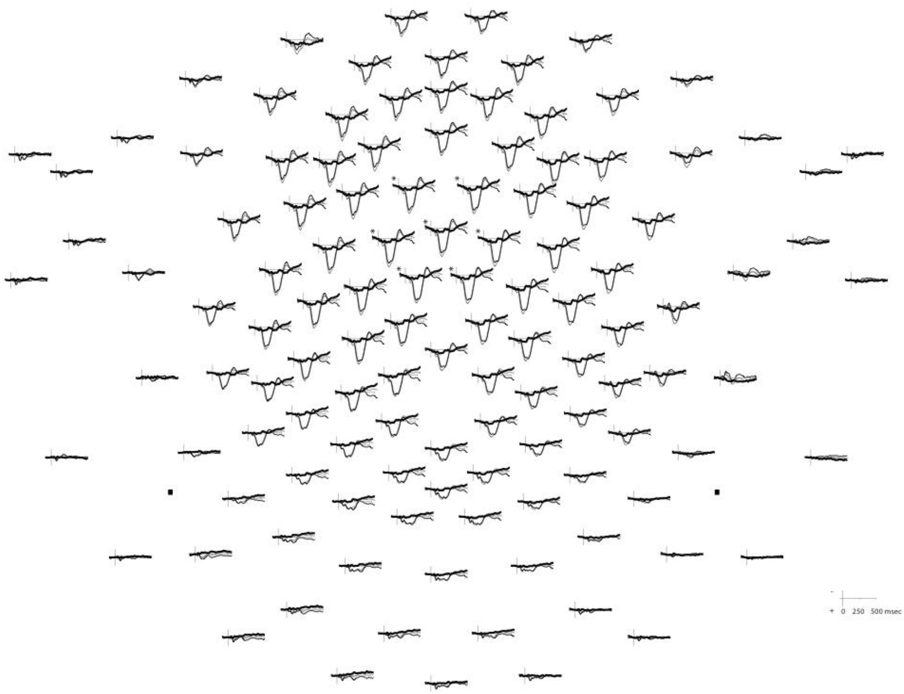


__Figure 14__. Grand average ERPs for all electrodes, with mastoid reference, showing responses to standards and a deviant average (based on four deviants: intensity, gap, location, and pitch) and the corresponding MMN difference wave (standard response subtracted from deviant average response). Electrodes used in statistical analyses are marked with stars. Mastoid references are marked with squares. Negative values are towards the top of the figures. (Illustration by Petter Kallioinen, co-author of Paper I–IV; previously not published.)

5.1.2 Time windows

Paper I includes a visual inspection of the waveforms. The visual evaluation of the standard responses resulted in selection of four TWs for further analyses, see *Table 6* and *Figure 15*.

Table 6. *Summary of the time windows (TWs) created in Paper I.*

Time windows	Time interval	Characteristics
TW 1	0–80 ms	Between sound onset and before the large positive response
TW 2	80–220 ms	Interval of interest for MMN; the broad positive peak
TW 3	220–400 ms	Pronounced negativity
TW 4	400–500 ms	Positive slope

The characteristics are based on average responses to standard stimulus from 7 fronto-central electrodes. (By Elisabet Engström; previously not published.)

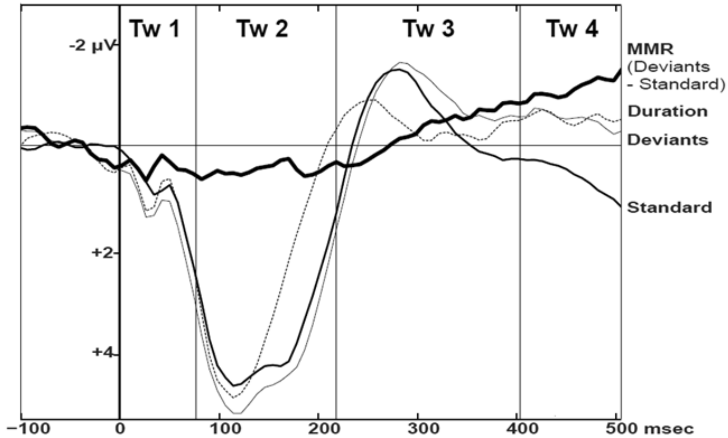


Figure 15. *The average responses to standards and the deviants (mean) from the fronto-central group of seven electrodes, negative values are towards the top of the figures. The 500 ms post-stimulus period is divided into four time windows (TWs), accordingly to the major positive and negative deflections in the standard condition. MMR, mismatch response. Figure adapted from Paper I, (Uhlen et al., 2017). 2017 by Scandinavian Psychological Associations and John Wiley & Sons Ltd. Reprinted with permission.*

5.1.3 Obligatory responses and mismatch negativity

Figure 16 displays the obligatory responses and MMN in all three groups: the children with NH, HA and CI. Statistically significant results from the analyses are listed below:

TW 1:

- The NH and CI groups had significantly larger obligatory responses to all stimuli (average; standard and deviants) than the HA group.
- Mismatch response of the gap deviant was significantly more positive than the standard stimulus. There were no interactions with the groups.

TW 2:

- The NH group had significantly larger obligatory responses to all stimuli (average; standard and deviants) than the HA group.
- Mismatch response of the gap and pitch deviants were significantly more positive than the standard stimulus, thus showing pMMRs. There were no interactions with groups.
- The duration deviant was significantly more negative than the standard stimulus, thus showing an MMN. There were no interactions with groups.
- The intensity deviant showed a significant group interaction with MMN in the HA group and pMMR in the CI group.
- The intensity and location deviants correlated negatively with age, with a transition to MMN in older subjects, especially in the NH group.

TW 3 and 4:

- The difference wave showed negative slopes for the NH and HA groups, but positive for the CI group. Location deviant showed a significant group interaction, where the CI group differed from the NH and HA groups.

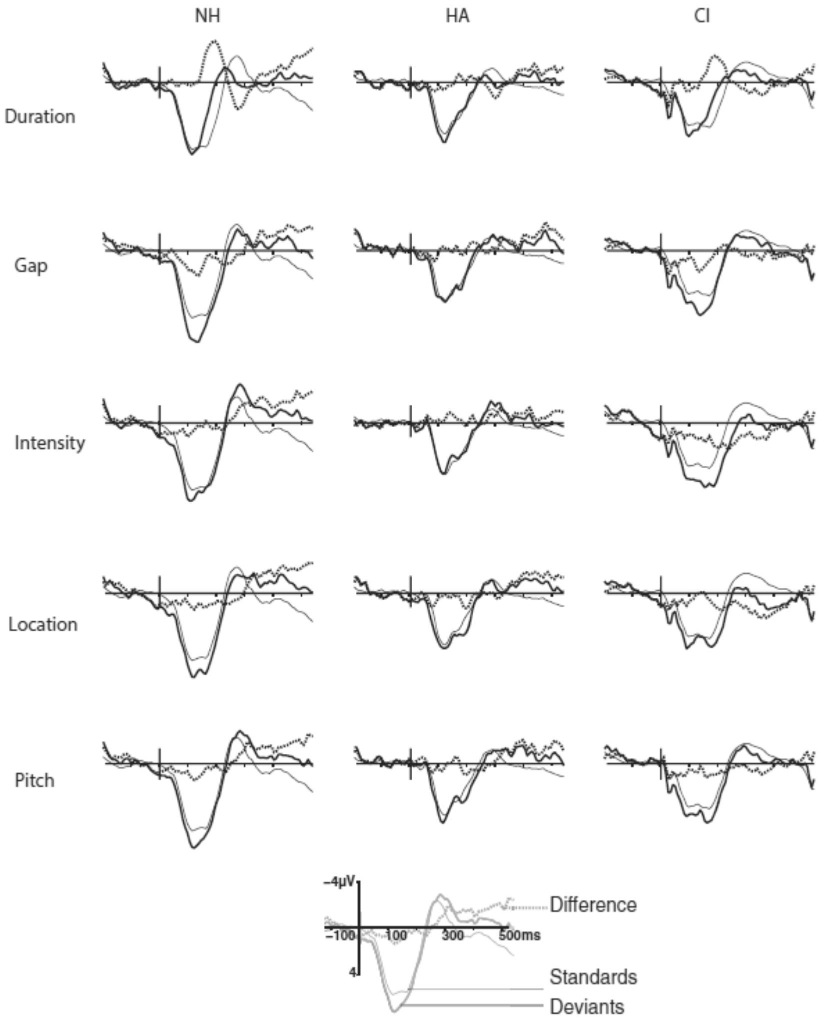


Figure 16. *The average responses from a fronto-central electrode to standard (thin line), the deviants (thick line), and the MMNs (dotted line) in the normal hearing (NH), hearing aid (HA), and cochlear implant (CI) groups, all deviants: duration, gap, intensity, location, and pitch. Negative values are towards the top of the figures. Figure from Paper I, (Uhlen et al., 2017). 2017 by Scandinavian Psychological Associations and John Wiley & Sons Ltd. Reprinted with permission.*

5.1.4 Main findings

The multi-feature paradigm, Optimum-1, elicited responses in children with HL using their HAs or CIs. Four TWs were created to structure further analyses. TW 2 within 80–220 ms was considered appropriate for the primary test of MMN effects.

Overall, the response amplitudes were smaller in the HA group compared to the NH group in TW 1 and TW 2. Otherwise, the results could not statistically prove any major differences in discrimination between groups. There was a high degree of inter-individual variability with both MMNs and pMMRs.

5.2 PAPER II

The purpose of this study was to investigate whether the computer-assisted reading intervention programme with a phonic approach, GraphoGame, could have a positive effect on the ability to hear and discriminate small changes in auditory stimulation by examining ERP and MMN among children with HAs (n=15). Children with NH (n=14) constituted the reference group.

ERP recordings were performed before and after one month of repeated training. The multi-feature paradigm, Optimum-1 (Naatanen et al., 2004), measuring five deviants (gap, intensity, pitch, location, duration) and a standard stimulus, was used.

The obligatory responses in ERP and the corresponding MMN of all deviants were analysed in both groups. Data refers to the mean ERP amplitudes (µV) in the time interval 80–224 ms, thus, equal to TW 2 in **Paper I**, which corresponds to the large positivity of the standard stimulus (visually checked) and includes the period of a typically MMN peak between 160–220 ms (Luck, 2014). Since both MMN and pMMR were present, these findings have been described separately. Finally, the performance result of the GraphoGame intervention is presented.

5.2.1 Obligatory responses

Figure 17 consists of raw waveforms from EP Toolkit/MATLAB® and presents each deviant and standard stimulus on the group level, meaning the HA group versus the NH group.

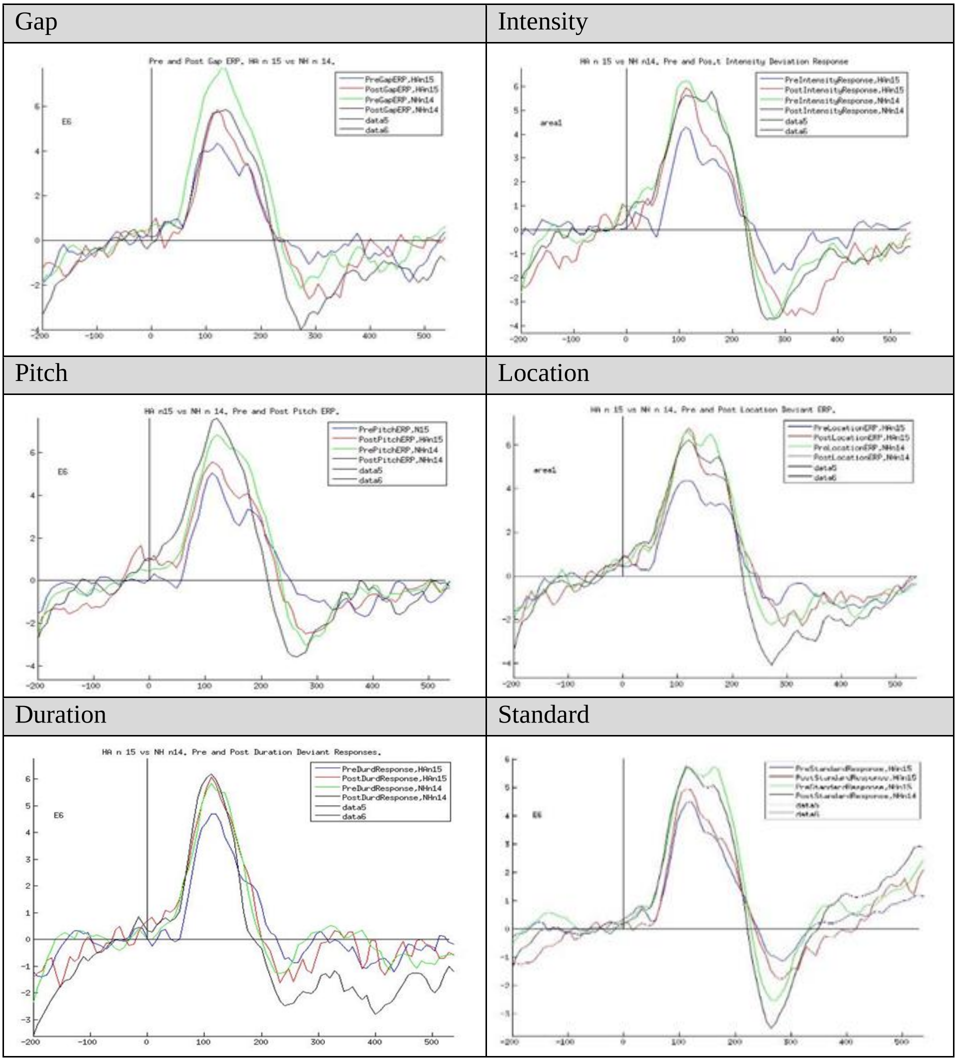


Figure 17. *Raw data; waveforms from EP Toolkit/MATLAB®. Obligatory responses in all deviants (duration, intensity, location, pitch, gap) and standard presented in groups: children with hearing aids (HAs) versus children with normal hearing (NH).*
Blue line: children with HA before (pre) training; green line: children with NH before (pre) training; red line: children with HA after (post) training; black line: children with NH after (post) intervention. X axis: time (ms); Y axis: amplitude (µV). (Illustration by Elisabet Engström; previously not published.)

Testing for the simple main effects of group, meaning testing for differences in ERP response between groups at different time points (before and after training), revealed a statistically significant difference in mean ERP response between the HA and NH groups before training, but this difference disappeared after training.

Testing for the simple main effects of time means observing the differences in ERP response between time points for each category of the between-subject factors (groups). In the NH group, mean ERP responses were not statistically significantly different before versus after training, The HA group showed a tendency towards higher mean ERP response after training, although not statistically significant (p = .095).

Figure 18 shows the mean ERPs before and after training in the NH and HA groups.

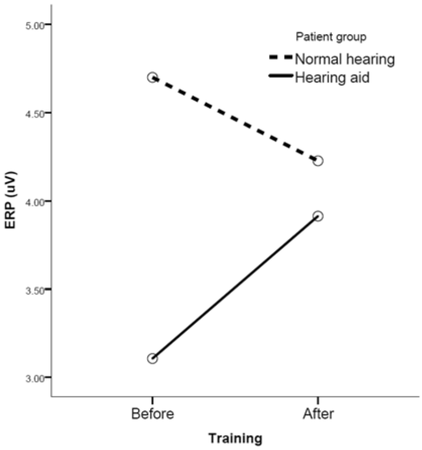


Figure 18. *Mean ERPs (mean amplitude of the obligatory responses, all deviants and standard) before and after training in hearing aid and normal hearing groups. ERP, event-related potential. Figure from Paper II, (Engstrom et al., 2019). 2018 by Elsevier B.V. Reprinted with permission.*

5.2.2 Mismatch negativity

There was a statistically significant difference in MMN between the HA and NH groups before training, but this difference between groups disappeared after training. However, no significant differences in MMN were demonstrated before versus after training, neither among the children with HA nor the children with NH. The mean amplitude MMNs of each deviant are shown in *Figure 19* (children with NH) and *Figure 20* (children with HAs).

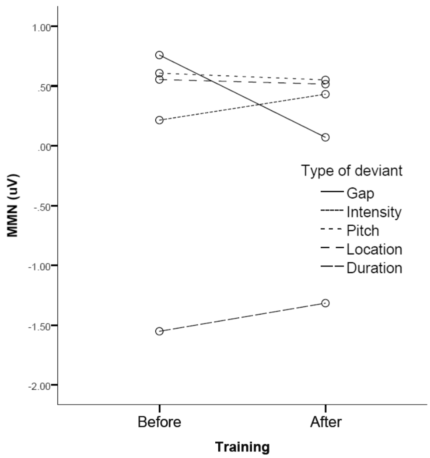


Figure 19. *MMNs (mean amplitude) of the five deviants before and after training in the normal hearing group. MMN, mismatch negativity. Figure from Paper II, (Engstrom et al., 2019). 2018 by Elsevier B.V. Reprinted with permission.*

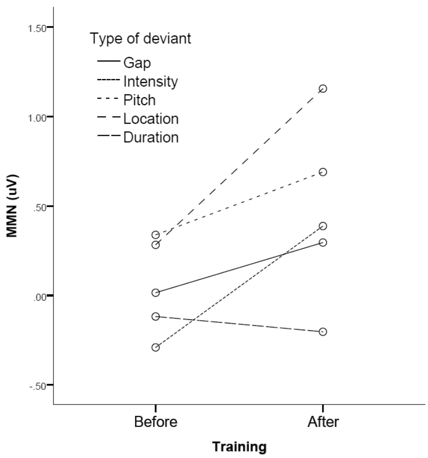


Figure 20. *MMNs (mean amplitude) of the five deviants before and after training in the hearing aid group. MMN, mismatch negativity. Figure from Paper II, (Engstrom et al., 2019). 2018 by Elsevier B.V. Reprinted with permission.*

5.2.3 Mismatch negativity and positive mismatch response

In this section, the term MMNs only refers to negative mismatch responses. Positive responses are referred to as pMMRs.

Before training, only 2 of all children showed MMNs in all five deviants, whereas 6 children had purely pMMRs. After training, 4 of the children presented only MMNs in all deviants, whereas 4 children had pMMRs in all deviants. When starting with MMN before training, there was visually a tendency to a change towards a positive value after training, see *Figure 21*. When having a pMMR before training, a greater diversity was shown, either changing to a more positive pMMR or a more negative value, even an MMN, see *Figure 22*.

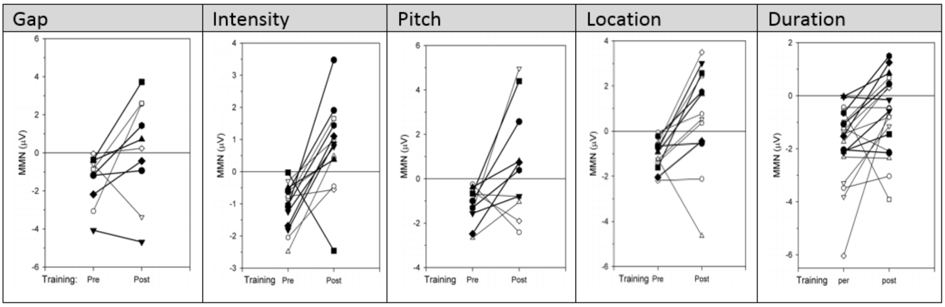


Figure 21. *Subjects with MMN before training. Filled symbols with thick lines are children with hearing aids; white symbols with thin lines are children with normal hearing. MMN, mismatch negativity; pre, before training; post, after training. Figure regarding the gap deviant (first box) reprinted from Paper II, (Engstrom et al., 2019). 2018 by Elsevier B.V. Reprinted with permission. (Illustration otherwise by Elisabet Engström; previously not published.)*

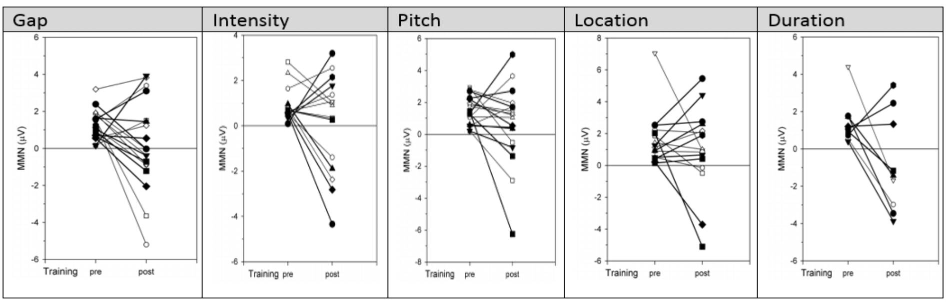


Figure 22. *Subjects with pMMR before training. Filled symbols with thick lines are children with hearing aids; white symbols with thin lines are children with normal hearing. pMMR, positive mismatch response; MMN, mismatch negativity; pre, before training; post, after training. Figure regarding the gap deviant (first box) reprinted from Paper II, (Engstrom et al., 2019). 2018 by Elsevier B.V. Reprinted with permission. (Illustration otherwise by Elisabet Engström; previously not published.)*

5.2.4 Performance results in GraphoGame

Training was the main purpose of GraphoGame, but the following performance results are also worth mentioning.

Only 6 children with HAs reached the maximum level (56) compared to 8 of the NH children. Less than half (46%) of the children with HAs, but most of the NH children (79%), achieved more than level 39 (70 % of the maximum level; delimitation from the plots, see also *Figure 31* in *5.3.4 Performance results in GraphoGame*). The children with HAs achieved the lowest results overall (1 child: level 5; 5 children: level 11–18). The lowest level among the NH children was 27. Although children with more severe HL did not achieve any top levels in

GraphoGame, the statistically the severity of HL did not show any significant correlation to the performance results. For an overview of the performance results among the children with HA, see *Figure 23*.

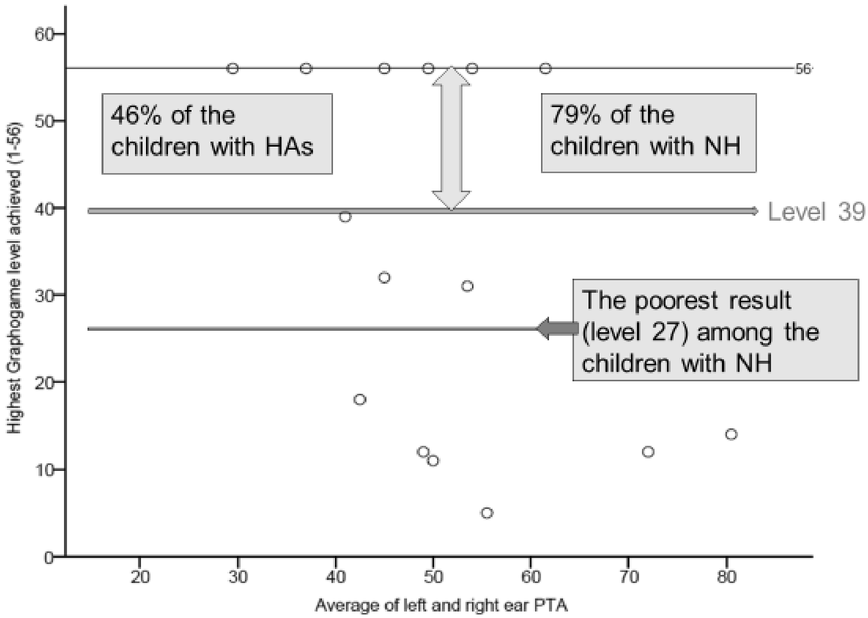


Figure 23. *Achieved levels in GraphoGame regarding the children with hearing aids (HAs; the individual plots) and normal hearing (NH). Pure tone average (PTA4) refers to hearing levels in the children with HAs. Figure adapted from Paper I, (Engstrom et al., 2019). 2018 by Elsevier B.V. Reprinted with permission.*

5.2.5 Main findings

The main findings set out in **Paper II** were the significant differences in both the obligatory responses in ERP and MMN between the NH and HA groups before the computer-assisted training, which disappeared after the intervention. This suggests possible effects resulting from training among the children with HAs. The presence and mix of MMN and pMMR from all deviants in each group (NH vs HA) were highlighted.

5.3 PAPER III

The design of **Paper III** follows **Paper II**. The main difference is the procedure in the electrophysiological processing, due to specific CI artefact corrections in **Paper III**. Thus, **Paper III** investigated whether the computer-assisted reading intervention programme with a phonic approach, GraphoGame, could affect ERP and MMN in children with CIs (n=15). Children with NH (n=14) participated as a reference group (the same NH group as in **Paper II**).

Similar to **Paper II**, ERP recordings were performed before and after one month of repeated training, and the multi-feature paradigm, Optimum-1 (Naatanen et al., 2004), was used. Furthermore, the results of the obligatory responses in ERP and the corresponding MMN of all deviants were analysed in both the CI and NH groups. Data refers to the mean ERP amplitudes (µV) in the time interval 80–224 ms, that is, TW 2 in **Paper I**, which includes the period of a typically MMN peak between 160–220 ms (Luck, 2014). Both MMN and pMMR were present, and a separate description of these findings are outlined below. The performance result in GraphoGame is briefly presented in the end.

Figure 24 (next page) displays the obligatory responses and MMN in each deviant (duration, gap intensity, location, and pitch); for both groups (the children with NH and CIs); and, before and after training.

5.3.1 Obligatory responses

No significant differences in mean obligatory responses between groups (CI vs NH) were observed, neither before nor after training. There was no statistically significant difference in obligatory responses after training within each group. *Figure 25* shows the mean ERPs before and after training in the CI and NH groups. There was no significant three-way interaction, meaning there were no interactions between type of deviant, before and after training and whether CI or NH.

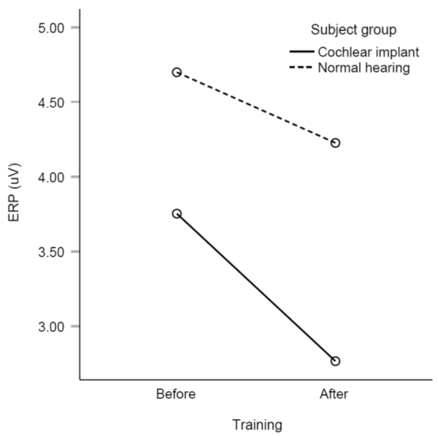


Figure 25. *Mean ERPs (mean amplitude of the obligatory responses, all deviants and standard) regarding before and after training in cochlear implant and normal hearing groups. ERP, event-related potential. Figure from Paper III, (Engstrom et al., 2020). Reprinted under CC BY.*

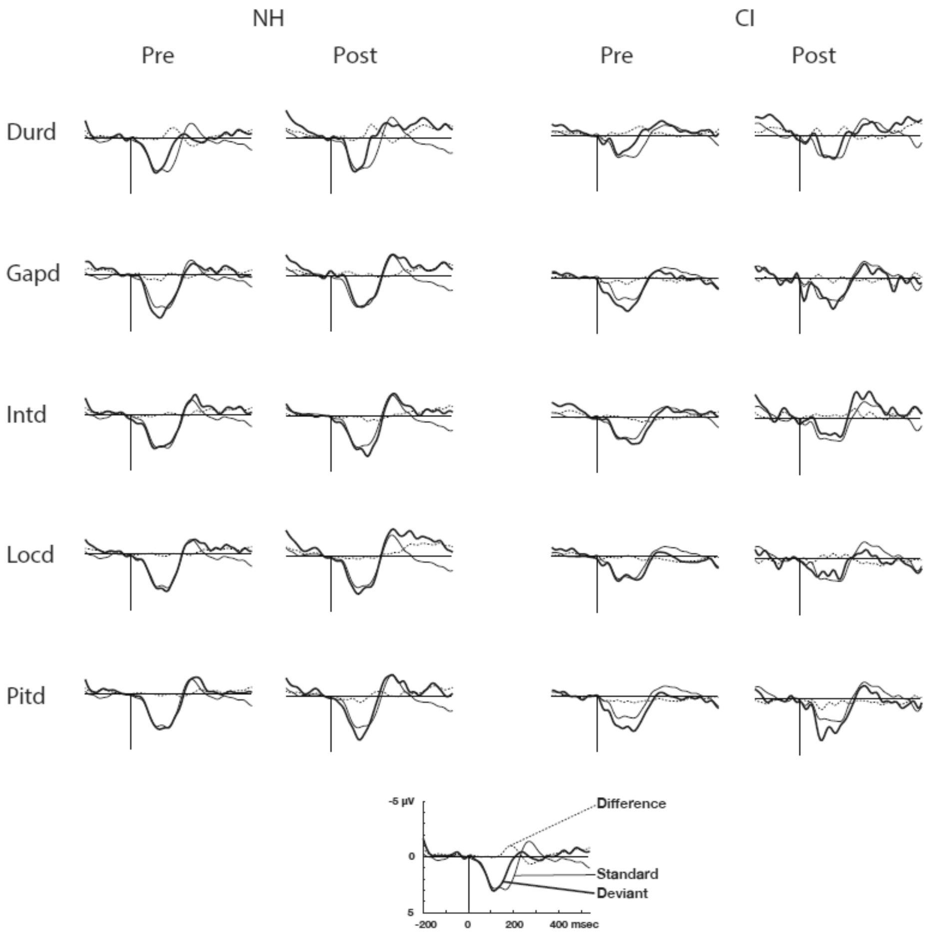


Figure 24. *The average responses from a fronto-central electrode to standard (thin line), the deviants (thick line), and the MMNs (dotted line) in the normal hearing (NH) and cochlear implant (CI) groups, before (pre) and after (post) training, all deviants. Durd, duration deviant; Gapd, gap deviant; Intd, intensity deviant; Locd, location deviant; Pitd, pitch deviant. Negative values are towards the top of the figures. Figure from Paper III, (Engstrom et al., 2020). Reprinted under CC BY.*

5.3.2 Mismatch negativity

There was no significant difference in mean MMN between the CI and NH groups, neither before nor after training. There was no statistically significant difference in MMN after training among the children with CIs or NH. *Figure 26* shows the MMN of each deviant before and after training in the CI group. For MMN regarding the children with NH, see *Figure 19, 5.2.2 MMN*.

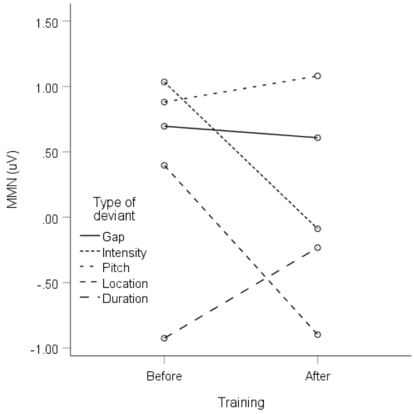


Figure 26. *MMNs (mean amplitude) of all deviants before and after training in the cochlear implant group. MMN, mismatch negativity. Figure from Paper III, (Engstrom et al., 2020). Reprinted under CC BY.*

5.3.3 Mismatch negativity and positive mismatch response

In this section, the term MMNs only refers to negative responses, and the positive responses are referred to as pMMRs.

Individually, there was a mix between MMN and pMMR in both the CI and NH groups. *Figure 27* illustrates the diversity in responses (MMNs and pMMRs) before training. For example, 2 children (1 CI and 1 NH) showed MMNs in all deviants before training, whereas 4 children (2 CI and 2 NH) had exclusively pMMRs. An analogous mix of MMNs and pMMRs after training is shown in *Figure 28*; here 2 children (1 CI and 1 NH) showed purely MMNs, and 2 children with CI showed only pMMRs.

In those participants with MMN before training, a tendency to more positive values, even pMMRs, was observed after training. On the contrary, having a pMMR before training, implied more negative values after training. The same pattern, or tendency, was observed in all deviants and was visually most distinct for the change from an initial pMMR, whereas the change from an initial MMN demonstrated some diversity. For an illustration, the changes of all five deviants are individually drafted, accordingly to either MMN, see *Figure 29*, or pMMR, see *Figure 30*, before training.

These results must be interpreted with caution due to the small sample sizes.

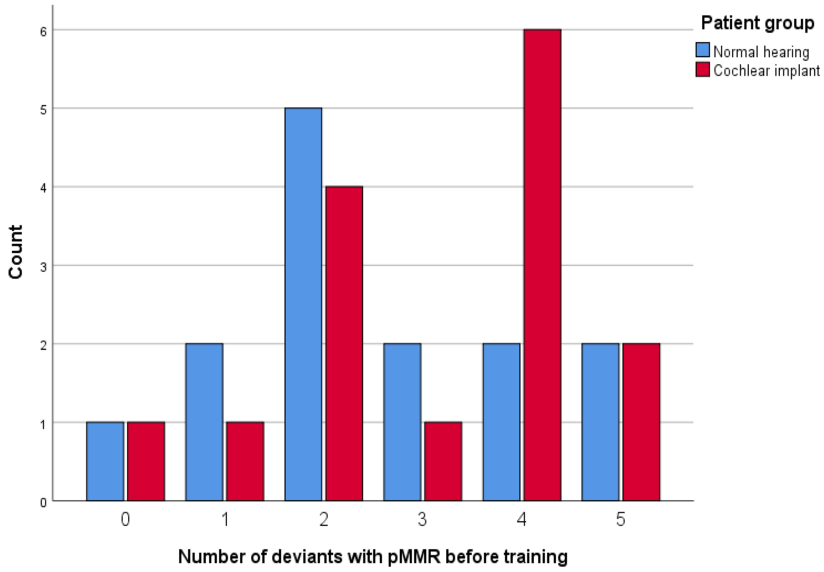


Figure 27. *Number of deviants with pMMR before training in the cochlear implant (red) versus normal hearing (blue) groups. No (0) pMMR means all (5) deviants have MMNs; 1 pMMR means having 4 MMNs, and so on. pMMR, positive mismatch response. (By Elisabet Engström; previously not published.)*

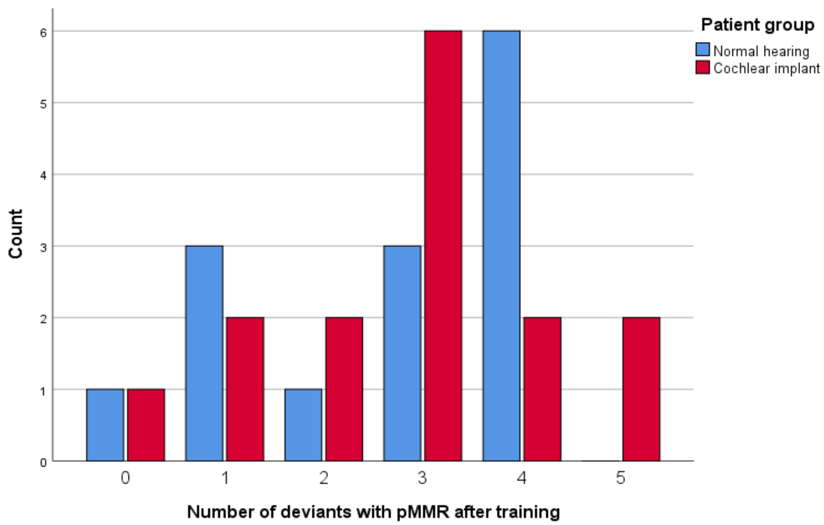


Figure 28. *Number of deviants with pMMR after training in the cochlear implant (red) versus normal hearing (blue) groups. No (0) pMMR means all (5) deviants have MMNs; 1 pMMR means having 4 MMNs, and so on. pMMR, positive mismatch response. (By Elisabet Engström; previously not published.)*

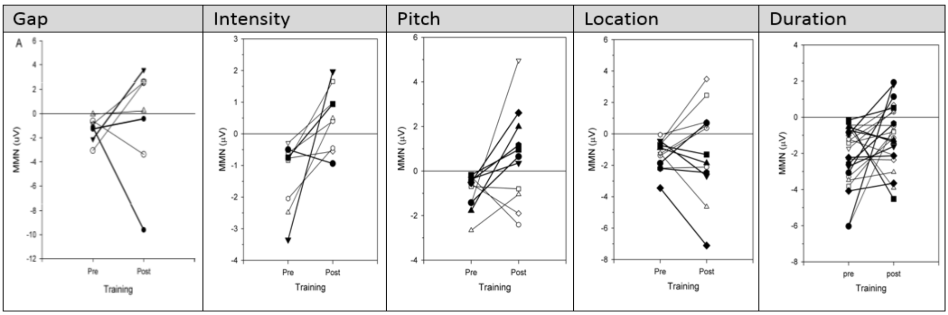


Figure 29. *Subjects with MMN before training. Filled symbols with thick lines are children with cochlear implants; white symbols with thin lines are children with normal hearing. MMN, mismatch negativity; pre, before training; post, after training. Figure regarding the intensity deviant (second box) reprinted from Paper III, (Engstrom et al., 2020). 2018 by Elsevier B.V. Reprinted with permission. (Illustration otherwise by Elisabet Engström; previously not published.)*

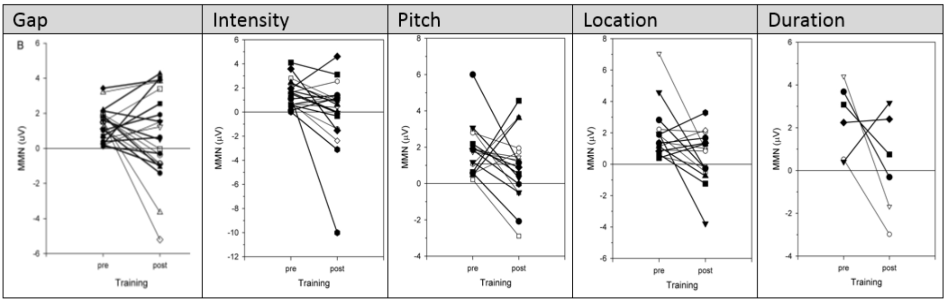


Figure 30. *Subjects with pMMR before training. Filled symbols with thick lines are children with cochlear implants; white symbols with thin lines are children with normal hearing. pMMR, positive mismatch response; MMN, mismatch negativity; pre, before training; post, after training. Figure regarding the intensity deviant (second box) reprinted from Paper III, (Engstrom et al., 2020). 2018 by Elsevier B.V. Reprinted with permission. (Illustration otherwise by Elisabet Engström; previously not published.)*

In those participants having MMNs or pMMRs before training, a few statistically significant differences were observed:

- Mean MMN for the pitch deviant was statistically different before versus after training in the CI group, though, changing to more positive values (even pMMR).
- Mean MMN for the intensity deviant was statistically different before versus after training in the NH group, also changing to more positive values (even pMMRs).
- Mean pMMR for the duration deviant was statistically different between the CI versus NH group after training. This resulted from more negative MMN values after training in the NH group.

5.3.4 Performance results in GraphoGame

In the CI group, 6 children reached the highest level in GraphoGame, equal to the HA group. Overall, the CI children achieved better results than the HA children. Only 2 children achieved levels under 20 (level 9 and 13), for an illustration, see *Figure 31*. It was not possible to statistically demonstrate any significant correlations in performance of GraphoGame with age, age of hearing, age of implantation or hearing thresholds. There were no significant relations to sex or type of HL.

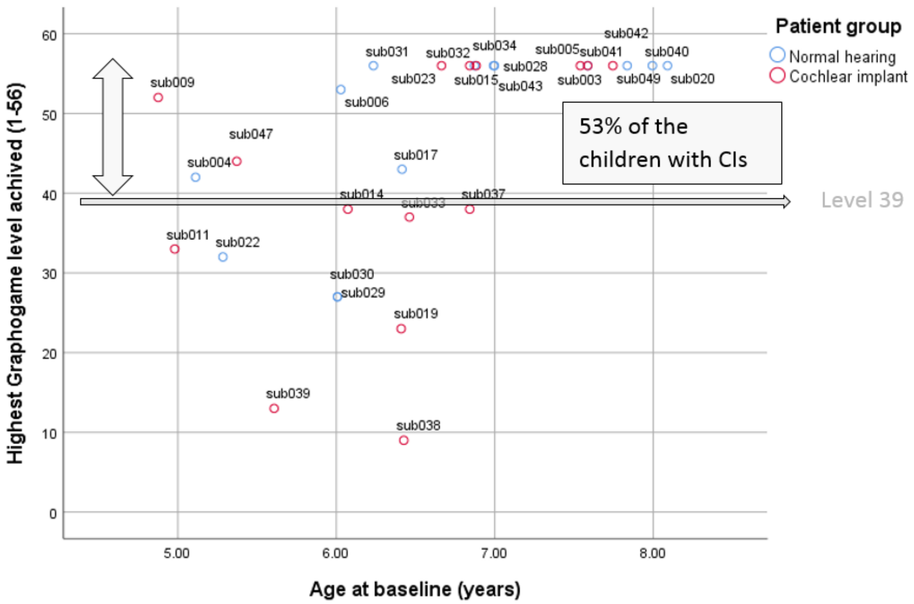


Figure 31. *Achieved levels in GraphoGame regarding the children with cochlear implants (CIs; red) and normal hearing (blue). (Illustration by Elisabet Engström; previously not published.)*

5.3.5 Main findings

The results in **Paper III** could not statistically demonstrate any significant computer-assisted training effects on ERP and MMN among children with CIs. These results differed from the results regarding children with HAs in **Paper II**, suggesting differences between these two subgroups of children with HL. The paper also offered a description of MMN and pMMR regarding all deviants in each group (NH vs CI).

5.4 PAPER IV

All participating children in the original study (**Paper I**) were invited to this three-year follow-up study. The aim of this study was to examine how ERPs and MMN change over time among children with HL using HAs (n=7) or CIs (n=6). Children with NH (n=10) participated as a reference group.

The electrophysiological recordings followed the same procedure from three years earlier, and the same equipment was used. The multi-feature paradigm, Optimum-1 (Naatanen et al., 2004), was used. The results of the obligatory responses in ERP and the corresponding MMN of all deviants were analysed in all three groups; the children with HAs, CIs and NH. Data refers to the mean ERP and MMN amplitudes (µV) in the time interval 80–224 ms, that is the same time interval analysed in **Paper II and III** and based on TW 2 in **Paper I**. Due to the limited number of children, it was not reasonable to divide the groups into even smaller subgroups. Therefore, the results of MMN are not further analysed regarding MMN versus pMMR.

Figure 32 displays the obligatory responses and MMN in each deviant (duration, gap intensity, location, and pitch), in all groups (the children with NH, HAs and CIs), at baseline as compared to the follow-up after three years.

5.4.1 Obligatory responses

At baseline, the mean of the obligatory responses in ERP was significantly greater in the NH group compared to the HA group. At follow-up, the mean of the obligatory responses in ERP was significantly lower in the CI group compared to both the HA and NH groups. The HA group showed a significant change (increasing mean amplitudes) between baseline and follow-up. For an illustration of the obligatory responses in each group, see *Figure 33*.

Analysing each deviant demonstrated a few differences: the mean amplitude of the location deviant was significantly lower in children with CIs at follow-up compared to baseline. The gap deviant was significantly lower in the HA group compared to the NH and CI groups at baseline.

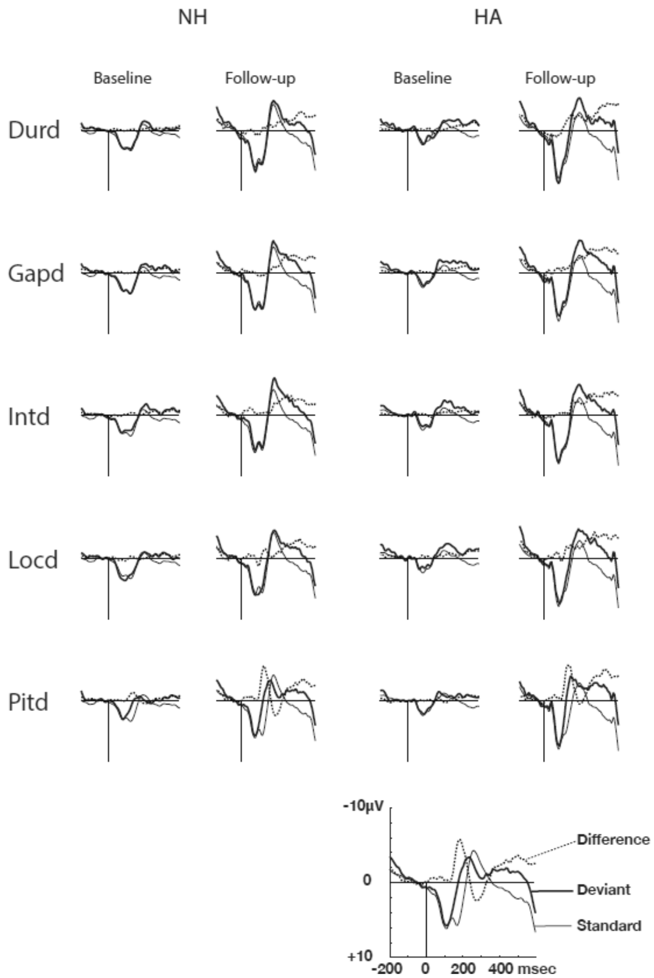


Figure 32. *The average responses from a fronto-central electrode (number 6, near Fz) to standard (thin line), the deviants (thick line) and MMN (dotted line), all deviants and groups (NH, HA and CI), at baseline and at follow-up. Durd, duration deviant; Gapd, gap deviant; Intd, intensity deviant; Locd, location deviant; Pitd, pitch deviant; NH, normal hearing; HA, hearing aid; CI, cochlear implant. Negative values are towards the top of the figures. Figure from Paper IV, (Engstrom et al., 2021). Reprinted under CC BY.*

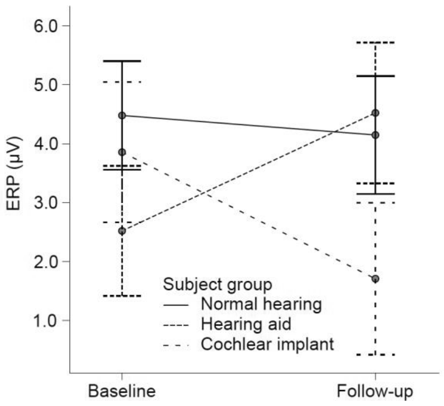


Figure 33. *Mean ERPs (mean amplitude of the obligatory responses, all deviants and standard) in the normal hearing, hearing aid and cochlear implant groups at baseline and after three years. ERP, event-related potentials. Figure from Paper IV, (Engstrom et al., 2021). Reprinted under CC BY.*

5.4.2 Mismatch negativity

Analyses of mean MMN could not statistically demonstrate any changes over time or between groups. The only significant interaction found in ANOVA was the interaction between the duration deviant and time in the HA group. *Figures 34–36* show the MMN of each deviant in all three groups (NH, HA vs CI).

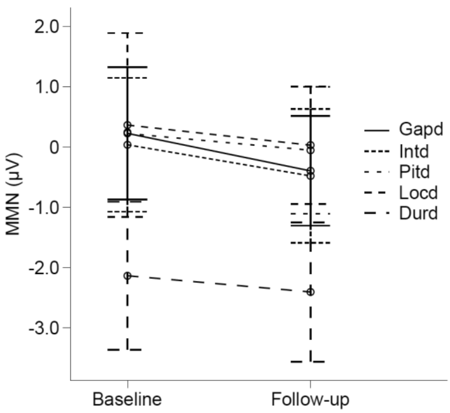


Figure 34. *MMNs (mean amplitudes) of all deviants at baseline and 3-year follow-up in the normal hearing group (n=10). Error bars are 95% confidence intervals. MMN, mismatch negativity; Durd, duration deviant; Gapd, gap deviant; Intd, intensity deviant; Locd, location deviant; Pitd, pitch deviant. Figure from Paper IV, (Engstrom et al., 2021). Reprinted under CC BY.*

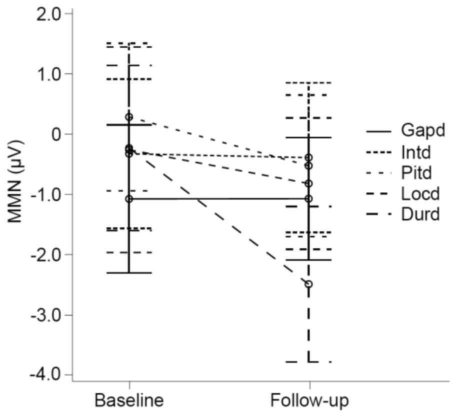


Figure 35. *MMNs (mean amplitudes) of all deviants at baseline and 3-year follow-up in the hearing aid group (n=7). Error bars are 95% confidence intervals. MMN, mismatch negativity; Durd, duration deviant; Gapd, gap deviant; Intd, intensity deviant; Locd, location deviant; Pitd, pitch deviant. Figure from Paper IV, (Engstrom et al., 2021). Reprinted under CC BY.*

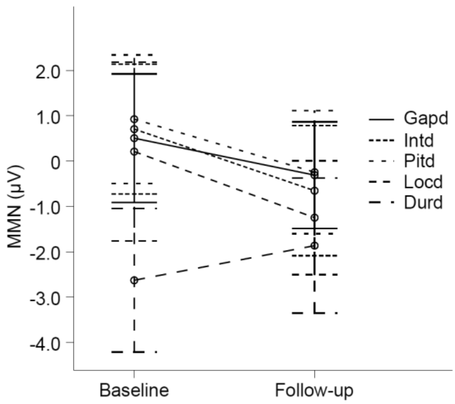


Figure 36. *MMNs (mean amplitudes) of all deviants at baseline and 3-year follow-up in the cochlear implant group (n=6). Error bars are 95% confidence intervals. MMN, mismatch negativity; Durd, duration deviant; Gapd, gap deviant; Intd, intensity deviant; Locd, location deviant; Pitd, pitch deviant. Figure from Paper IV, (Engstrom et al., 2021). Reprinted under CC BY.*

5.4.3 Main findings

The main finding in **Paper IV** was the significant change in mean ERP at baseline compared to follow-up in the HA group. This suggests a possible catch-up over time among the children with HAs. On the contrary, the obligatory responses in ERP among the children with CI were significantly lower than both the children with NH and HAs after three years, indicating poorer development of the central auditory system among the children with CIs.

6 DISCUSSION

The children with HL and ERP recordings run like a common thread through all papers, and, additionally, **Paper II and III** include an intervention part. The discussion will therefore be general, covering all papers, unless otherwise stated. The main discussion points are the results in the light of the participants and the method, including ERP, MMN and the choice of stimuli. Maturational issues also need to be emphasised. Finally, reflections about the intervention part follow.

However, first, here is a brief summary of the main hypotheses set out in the papers:

- The hypothesis outlined in the first study, **Paper I**, was that the multi-feature paradigm Optimum-1 for eliciting ERPs and MMN could capture difficulties in perceiving small sound contrasts in children with HL using HAs or CIs.

- The hypotheses outlined in **Paper II and III** were that the computer-assisted reading intervention programme with a phonics approach would have a positive effect on the ability to hear and discriminate small changes in auditory stimulation among children with HL using HAs (**Paper II**) or CIs (**Paper III**), and, that these changes would be detectable by ERP and MMN.

- In the last study, **Paper IV**, the hypothesis was that ERPs and MMN would change over time among children with HL and that these changes might be different between children using HAs versus CIs, and also compared to children with NH.

Paper I demonstrated that the multi-feature paradigm Optimum-1 could elicit ERPs and MMN in children with HL using their HAs or CIs. The five deviants: gap, intensity, pitch, location, duration, are all basic features of speech, which are necessary for phonological skills; however, it was challenging to draw any conclusions from the analyses regarding the obligatory responses and MMN of each deviant, as there were no major differences between groups. When analysing the overall response amplitudes, they were significantly smaller in the HA group compared to the NH group in the interval feasible for analysis of MMN effects (TW 2). Lower amplitudes may reflect impaired discrimination of small changes in auditory stimulation.

In **Paper II**, it was not possible to statistically demonstrate a change after training in each group, but there was a difference between the groups (the children with HAs versus NH) before training. This difference disappeared after the intervention. In other words, children with HAs did receive amplitudes in obligatory response and MMN closer to those of the children with NH after training, suggesting possible training effects among the children with HAs. On the contrary, the obligatory responses among the children with NH were visually less prominent after training, however, not statistically significant, and hard to explain. The findings warrant further research. The small sample size and issues of the current maturational changes, meaning

MMN versus pMMR, complicate the analyses and interpretations. Interestingly, similar changes could not be seen among the children with CIs in **Paper III**. This may reflect better preconditions among the children with HAs and reduced plasticity in the central auditory system among the CI children. The results highlight the importance of distinguishing children with HL into HA and CI groups.

Based on the maturational changes and frequent occurrence of pMMRs, as well as the overall results in the first papers (**Paper I–III**), it was difficult to predict how ERP and MMN would change in the different groups after three years. However, it was reasonable to believe there would be differences between the groups. **Paper IV** demonstrated a significant difference in mean ERP at baseline compared to follow-up among the children with HAs, suggesting a possible to catch-up over time. Furthermore, the mean obligatory responses in the HA group was significantly lower compared to the NH group at baseline. The children with CIs presented mean obligatory responses in ERP significantly lower than both the children with HA and NH after three years, which may reflect poorer development. The duration deviant was the only deviant showing a change (increase) in MMN over time; this change was observed in the HA group. Otherwise, statistical significances could not be demonstrated regarding MMN.

In general, the obligatory responses seemed to better reflect changes and differences than MMN, and it was hard to draw any certain conclusions regarding the different deviants.

6.1 THE PARTICIPANTS

Overall, the number of children with HL is limited, and the group may be heterogeneous. For example, aetiology, degree of HL, affected frequencies, the onset of HL, age at HA fitting and age of CI surgery can vary. Hence, an effort was made to reduce diversity among the participating children with HL in these works. For example, the age range was less than three years and only patients with bilateral and symmetrical SNHL were included. Differences regarding aetiology and hearing did not show any correlations to the results in the children with HL.

Many of the participant HL medical histories were partially unknown, since OAE testing in new-borns was not yet part of the national hearing screening programme in Sweden when most of the participating children were born. In the future, information about the hearing situation from birth will be more reliable, thanks to the implementation of the national hearing screening programme.

The age span at the baseline study (ERP 1) was 5–8 years. The presence of pMMR in this age span was higher than expected, leading to further analyses, see Section *6.2.3 MMN and pMMR* below.

The dropout in the follow-up study (**Paper IV**) reduced the ability to demonstrate significant results.

Some children in the reference group were siblings to the children with HL. This reduced differences in, for example, socio-economic conditions, wordings, and language at home between the groups; however, these issues and possible effects were not further analysed.

6.2 THE METHOD

6.2.1 The method and design of the project

Given the design of the project, which was experimental in part, the reasons behind the choice of method should be explained.

6.2.1.1 Benefits

The advantages of MMN are many. MMN reflects discrimination ability and offers one neurophysiological building block of the phonological processing skills. It can be elicited regardless of whether the subject is paying attention to the stimuli or not, and, together with being non-invasive and safe, it can be considered as an appropriate method, especially for testing children in the age groups in this thesis. Furthermore, deviant sound can differ from the standard in several perceptual features (frequency, duration, intensity, location, and gap). Optimum-1 (Naatanen et al., 2004) surveys them all, which is an advantage as it is not given that each deviant is equally affected by HL, intervention or time. Optimum-1 also enables an efficient recording of ERP, thus offering relatively short test sessions. MMN is also considered to be elicited with high reliability (Kujala, Kallio, et al., 2001; Kujala & Naatanen, 2001). The sensitivity and specificity of MMN are 80–85% for detecting central processing skills in CI users, when testing consonant-vowel syllables, /ba/ versus /da/, meaning the presence of MMN indicates good auditory memory and discrimination skills (Singh et al., 2004). Previous research has observed differences in MMN between patients with HL and NH controls (Bishop, 2007; Calcus et al., 2019; Naatanen et al., 2017; Ponton et al., 2000). Altogether, the method was considered appropriate for testing children with HL.

6.2.1.2 Limitations and challenges

Researchers face challenges in how to analyse and interpret the results of ERP and MMN. Beyond the processing of the ERP recordings, such as sampling, filtering, segmentation, and artefact correction, decisions must be made regarding choices of latency and amplitude. Also, different deviants have to be evaluated since they cause different responses. Moreover, the technical equipment varies, including the number of electrodes. The results of MMN are sometimes compared to different speech recognition or behavioural tests, which also vary between countries, for example, Category of Auditory Performance (CAP) and Speech Intelligibility Rating (SIR) (Singh et al., 2004), Melodic Contour Identification (MCI) (Zhang et al., 2013), speech recognition with phonetically balanced French monosyllable words (Turgeon et al., 2014) and audiometric Speech Recognition Scores (SRSs) (Lonka et al., 2013). Different hearing devices (manufacturers and models) may be used but are considered equivalent.

In summary, it is difficult to compare results from different ERP and MMN studies, since they imply several options regarding the choice of stimuli, processing, analyses, and interpretations of the results.

6.2.2 Event-related potentials and mismatch negativity

The results in **Paper I** framed the analyses in **Paper II–IV** and the same model was used for analyses in these papers. Creating specific TWs was necessary since the waveforms showed no distinct MMN peaks. TW 2 was chosen for the analyses in the further papers, thus corresponding to the typically MMN peak regarding the literature (Luck, 2014) and covering the major positive peak in the standard response.

Looking at the individual waveforms (see *Figures 8–10,* Section *4.2.2.2 Electrophysiological processing and analyses of ERP data*), there should be no doubt there are challenges in drawing any individual conclusions from ERP and MMN, which still limits the use of ERP or MMN in clinical practice. However, on a group level, data becomes more reliable (for an illustration see waveforms based on groups in *Figure 17,* Section *5.2.1 Obligatory responses*). The sample size may seem small; however, results from several ERP and MMN studies, especially regarding patients with HL, are often based on a few patients, for example, 5 adults (Lonka et al., 2013), and around 20–30 patients (Liang et al., 2014; Singh et al., 2004; Turgeon et al., 2014; Zhang et al., 2013). However, results from small sample sizes must still be interpreted with caution. Furthermore, it may be difficult to statistically prove effects or differences between groups, after the intervention or over time. Thus, visually distinct differences cannot always be statistically verified, pointing to the need of further research and larger sample sizes.

All deviants generated responses and were generally reacting in similar ways. Slight differences could be statistically proven, and visually, the duration deviant was subtly different from the other deviants. In **Paper I**, the duration deviant was the only deviant showing MMN, though no group interactions. These findings are consistent with other studies indicating that the duration deviant elicits the most stable MMN in children and adults (Kathmann et al., 1999; Uwer & von Suchodoletz, 2000). However, given the results in **Paper I–IV**, it is hard to point out or recommend any specific deviant in examinations of patients with HL.

The main findings regarding the characteristics of the obligatory responses and MMN in **Paper I**, were the lower amplitudes in TW 1 and TW 2 in the children with HAs compared to the children with NH. The amplitude is an effect of loudness, suggesting insufficient amplification through the HAs. The children with CIs instead showed a broader P1 peak and visually less distinct waveforms, which probably resulted from CI artefacts.

Regarding the children with CIs, the signal processing technique of the implants limits the qualities, like location due to the affected interaural time difference (Eklof & Tideholm, 2018). The type and technique of HAs certainly also affect the results. In summary, the results are always constantly affected by the technique and the neurophysiological preconditions on an individual basis, but, on the other hand, are purely reflecting the hearing situation in each child. The results outlined in the papers show differences between the subgroups of children with HL, meaning the children with HAs versus CIs, and should be important to consider in future research.

It was not possible to statistically demonstrate any significant correlations in the change of the obligatory responses or MMN after training (**Paper II and III**) regarding age, age of hearing, age of implantation or hearing thresholds. Neither were there no significant relations to sex or type of HL. There could, however, still be correlations or relations, as the results must be interpreted with caution due to the small sample sizes.

6.2.2.1 Limitations and challenges

Concerning obligatory responses and MMN, only small individual changes are to be expected. Given the small sample size, the probability of demonstrating significant results is reduced.

When testing children, results of MMN are affected by maturational processes, meaning both MMN and pMMR may be present, which cause difficulties in interpretation data and handling of results, see Section *6.2.3 MMN and pMMR* below.

In ERP recordings, ‘clean’ data is of the essence, and it is desirable to reduce or eliminate movement artefacts. That means the children must sit as still as possible. Hence, an effort was made to do the test sessions as comfortable as possible. Furthermore, the children with CIs also have specific CI artefacts, which complicates the ERP processing with another step; the ICA-based procedure (Luck, 2014).

6.2.3 Mismatch negativity and positive mismatch response

MMN undergoes maturational changes. Results from previous studies infer that MMN is quite stable during childhood (Cheour et al., 2000) and that MMN stabilises at the age of 5 years (Gomot et al., 2000). However, both MMN and pMMR were widely spread among the children in present studies, despite the initial age range over 5 years (5–7 years). The extent of pMMRs was surprisingly high, which complicated interpretation of the results, as well as the statistical analyses. These are partly based on averages and means; thus, a mix between positive and negative values can result in sums close to zero. In **Paper I–III** descriptions of the mismatch responses, meaning MMNs and pMMRs, are provided. Thus, no subjects with pMMRs are excluded in any analyses (**Paper I–IV**).

Regarding the intervention (**Paper II and III**), the hypothesis was that GraphoGame could have a positive effect on the ability to hear and discriminate small changes in auditory stimulation among children with HL and that these changes would be detectable by ERP and MMN. Only small changes were to be expected, however, the results were partly disappointing, especially regarding the children with CI (**Paper III**), where no significant changes could be proven, neither in the obligatory responses in ERP nor in MMN. This can be attributed either to insufficient power to detect such small changes, or to a true non-existing effect. The results warranted the deeper analyses and descriptions of the mismatch responses (MMN and pMMR) provided in both **Paper II and III**.

Below, MMN specifically refers to negativity only, and is separated from pMMR.

The changes in MMN and pMMR after training visually differed between the children with HAs (**Paper II**) and children with CIs (**Paper III**). The changes were less diverging among the children with CI if having pMMR before training. On the contrary, the children with HAs showed more consistent results, when having MMN before training. The hypothesis was that training would improve the discrimination ability, thus enhancing MMN. However, due to the presence of both MMNs and pMMRs, there are alternative ways of interpreting the results. If having pMMR before training, responses would not necessarily be more negative if the training was effective. **Paper II and III** rather elucidate the difficulties, than give a certain answer on how to interpret the results. When dividing the children with HL into even smaller subgroups, that is, not only using HAs or CIs but also whether having MMN or pMMR in each deviant, the possibilities to statistically demonstrate any computer-assisted training effects detectable with ERPs and MMN were hindered by the small sample sizes.

At the three-year follow-up (**Paper IV**) the dropout caused too small sample sizes, making it difficult to divide the children into even smaller subgroups. Hence, the remaining children in **Paper IV** are not further analysed regarding MMN and pMMR. This may explain the lack of significances regarding the results of MMN (referring here to all mismatch responses), despite the significant results regarding the obligatory responses.

6.3 THE INTERVENTION

This intervention part involves **Paper II and III** and refers to the computer-assisted reading intervention programme with a phonics approach, GraphoGame.

With experiences from different ERP studies and reading disabilities, researchers at the University of Jyväskylä have contributed to develop GraphoGame, primarily to support children with reading disabilities (Saine et al., 2011) and dyslexia (Lyytinen et al., 2015; Lyytinen et al., 2009). GraphoGame is well-established, translated into Swedish, designed for the age-span of children participating in the present study, and ERP can be used as a method for evaluating its results. (Bach et al., 2013). Together, GraphoGame was considered an appropriate choice of intervention in this project. Furthermore, the children could do their training at home since the programme was available on the internet. The children in the present study were asked to practice ten minutes per day during a month. There may be other options regarding available training programmes but comparisons between different training programmes were beyond the aims of this thesis.

The relatively short training period (one month) reduced possible interactions with the normal age-related maturation of ERPs and MMN.

Since only modest changes were to be expected on an individual basis, small sample sizes generated difficulties to statistically prove possible training effects by using ERP recordings. However, based on results in **Paper II** differences in ERP and MMN were seen between children with HA compared to the children with NH, suggesting possible training effects. In

Paper III, the children with CI did not show similar results. Altogether, additional grounds for recommending, or advising against, the training programme are needed, and it is also of importance to consider a range of other factors, for example, language input (language available in the environment) and intake (language that is internalised). Behavioural data have demonstrated improved phoneme-grapheme correspondence after training with GraphoGame in children with HL (Nakeva von Mentzer et al., 2013). GraphoGame is also considered to support the learning-process of reading (Ojanen et al., 2015). Looking at the achieved levels in GraphoGame, potentials for improvement are preferably seen among the children with HL.

It was not possible to statistically demonstrate any significant correlations in performance of GraphoGame regarding age, age of hearing, age of implantation or hearing thresholds. There were no significant relations to sex or type of HL. These parameters would be of interest to study in a larger sample size.

Using a group without training would have been preferable; however, the number of children was limited. This prevented further statistical analyses, where a larger sample otherwise could have been divided into smaller subgroups. Furthermore, given their best intentions, the families specifically requested the intervention. GraphoGame has been found to show other benefits (Ojanen et al., 2015), and it was considered inappropriate to withhold the training from half of the participants. However, a reference group with age-matched children with NH made it possible to improve the evaluation of the results.

Finally, it must be emphasised that the computer-assisted training programme is to be regarded as a supplement and is not meant to replace other professional assistances or tools.

7 CONCLUSIONS

The overall aim of this thesis was to gain knowledge about children with HL and, in the longer term, contribute to their enhanced support. The studies focused on the central auditory pathways by recording ERP and MMN. The design of the project was experimental, and it also included an intervention part. Finally, a follow-up-study after three years was performed.

Considering the project in a broader context, there is obviously a considerable knowledge gap regarding neurophysiological conditions in children with HL. ERP and MMN are well-established research methods today. Nevertheless, the methods imply different options of interpretations and analyses. Due to a lack of previous studies regarding children with HL, we had to develop a model interpretation and analysis of the results (**Paper I**).

Paper II demonstrated that differences in both obligatory responses in ERP and MMN between the children with HAs versus NH disappeared after computer-assisted reading intervention, GraphoGame, suggesting a training effect among the children with HAs. A similar change could not be shown among the children with CIs (**Paper III**).

After three years (**Paper IV**) there was a significant change in ERP regarding the children with HAs, indicating a possible catch-up. The children with CI did not show similar development. On the contrary, their mean ERP was significantly lower compared to the children with HAs and NH after three years, indicating a diminished development of the central auditory system.

The results indicated that the obligatory responses might be more sensitive to reflect possible differences and changes than MMN. Maturational changes of MMN in current age span, as well as the CI artefacts, were aggravating circumstances complicating the analyses and interpretations of results. Furthermore, only small individual changes were to be expected after training (**Paper II and III**) and time (**Paper IV**). Together with the small sample sizes, the likelihood of demonstrating significant results was reduced. Despite the efforts, it was difficult to draw any certain conclusions regarding the impact of each deviant. Rather, the results support the need for using more than one deviant, since they individually seem to be affected differently.

Altogether, the findings in **Paper I–IV** highlight the complexity of the neurophysiological field in children with HL, and the need for further research.

8 POINTS OF PERSPECTIVE

The hearing situation among children with HL and the neurophysiological field are complex, and this thesis illuminates the need for further research. Some issues are listed below:

- In TW 4, the time interval 400–500 ms after stimuli, the difference wave differed between the groups; the NH and HA groups showed negative slopes, whereas the CI group positive difference waves (**Paper I**). However, this TW 4, involving the late discriminative negativity (LDN), corresponds to responses depending on endogenous factors and is thought to be related to higher neurocognitive processing, rather than the exogenous factors affecting the earlier auditory sensory responses. Data from this TW 4, as well as data from TW 3, are available, however, still not analysed.

- EP Toolkit/MATLAB® offers possibilities of further mapping of the auditory central pathways. For example, topography views can be selected in EP Toolkit. Additional data from the participants in this thesis is available for analyses.

- The mismatch responses may vary by different stimuli (Cheour et al., 2000). Since the auditory cortical responses seem to be affected differently by different stimuli, this might reflect a variation of the sensitivity in the auditory central system. It might be of interest to use other stimuli.

- In clinical practice, individuality is of the essence, but so far, MMN is not yet ready for individual use. Furthermore, the method is quite a time consuming, and the procedures would preferably be simplified. For example, it must be further investigated which stimuli are best to use and what time intervals to choose. The children with CIs also need special considerations due to the CI artefacts. Thus, future research might lead to a well-defined and easier model for ERP-recordings, such as the selection of one (or a few) deviant(s) for best clinical use; maybe different ones are needed in different age groups and subgroups of children with HL. Individually mapping the different deviants may be another alternative. In the longer term, ERP and MMN may be a tool for predicting which children need intensified support, contribute to an individually designed support, and also provide guidance regarding which technical equipment needs further improvement by the manufacturers.

- There are benefits using objective hearing tests, and ERP and MMN contribute to the knowledge regarding the central auditory pathways in children with HL. Furthermore, the method may also be helpful in hearing examinations of children with special needs, or children speaking other languages, who cannot perform speech audiometry tests. However, to start, a greater knowledge of group, or subgroup, level, is a good objective.

- Thanks to the neonatal hearing screening programme, including the OAE test, HA fitting can start within a couple of months and CI surgery is possible to accomplish under the age of one year. Thus, the hearing situation among children with HL today may differ from that of the children participating in this study. Hence, it would be of interest to reproduce the same testing today in children within the same age group. The neonatal hearing screening programme also contributes to better knowledge overall, by helping determine whether the child has been NH at birth or not. The medical history will be more certain and lead to improved statistics regarding possible correlations.

- Due to the maturational changes, a more persistent and long-term follow-up would be desirable, for example, annually visualising the transfiguration of MMN.

- Since **Paper IV** shows changes in ERP over time, as well as differences between groups (NH, HA, CI), it would be interesting to examine possible training effects also in higher age groups. Benefits from training programmes might be different in different ages, also depending on the subgroups of HL.

- Evaluating the results from neurophysiological recordings in comparison to behavioural tests and phonological processing skills may give another dimension of the hearing situation and central auditory pathways in children with HL.

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***

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***

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***

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***

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***

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